Positioning therapies in IBD *IN 2024*

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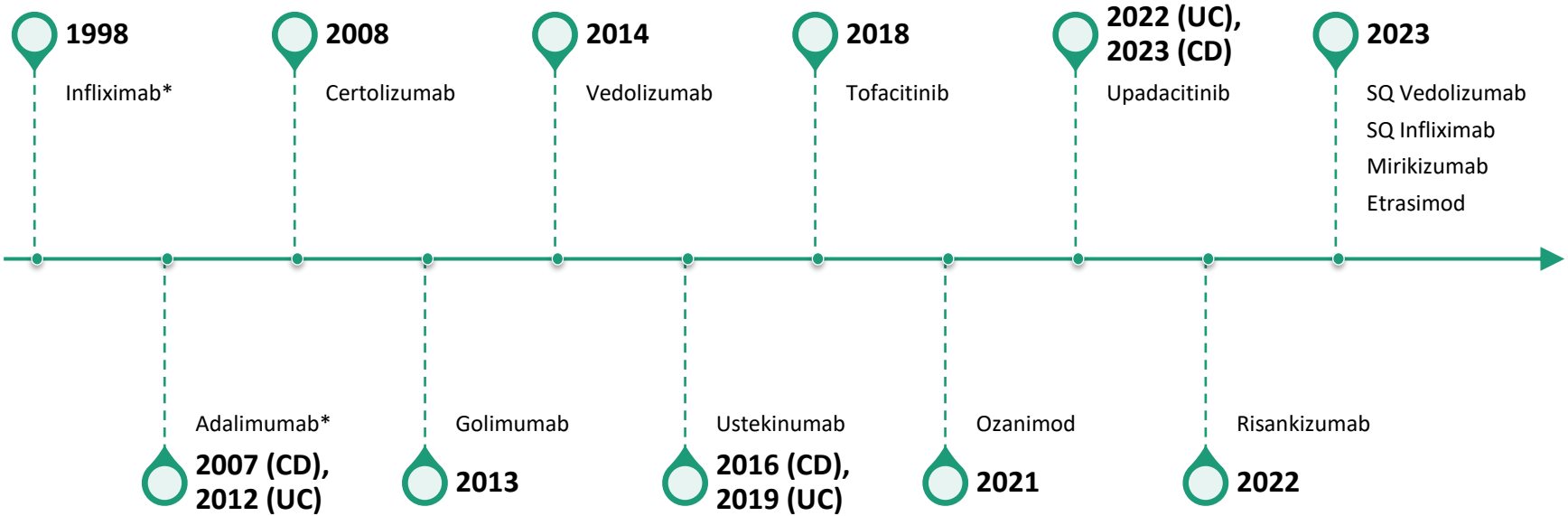
Disclosures

- OD: Consultant for Abbvie, Jannsen. Research Funding from Pfizer.

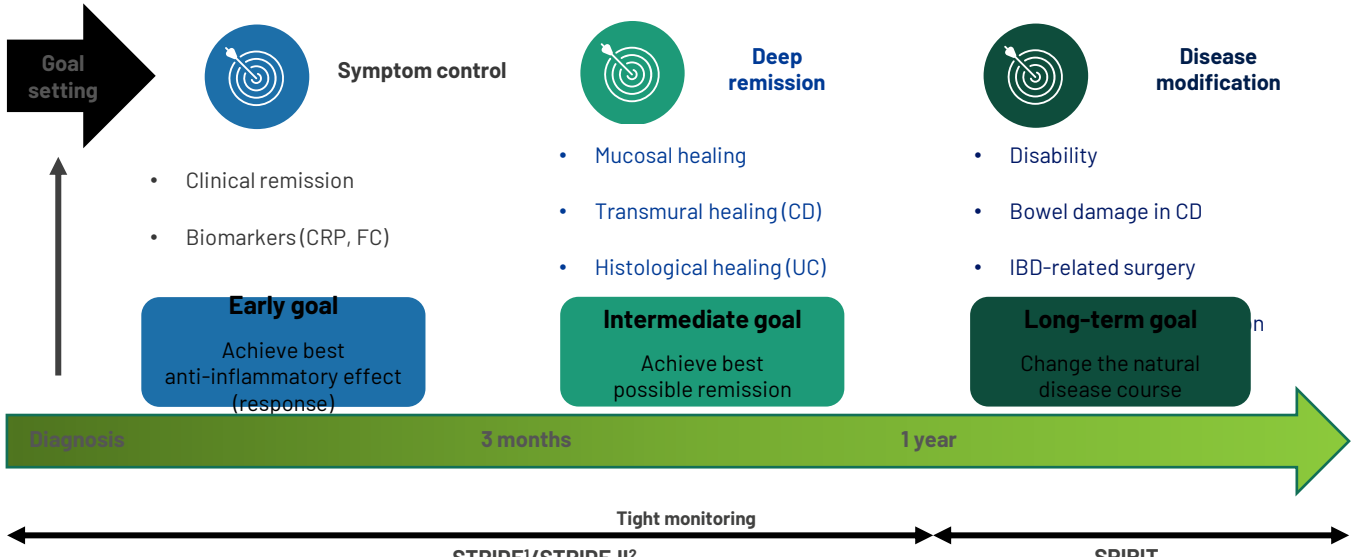
The history of treatment in IBD



What's new(ish)!

- Biosimilars
- SC VDZ
- SC IFX
- Etrasimod
- Mirikizumab
- Risankizumab
- Upcoming treatments

In Parallel, the Bar was Raised and Expectations Were Redefined in CD: Can we Modify the Course of the Disease?

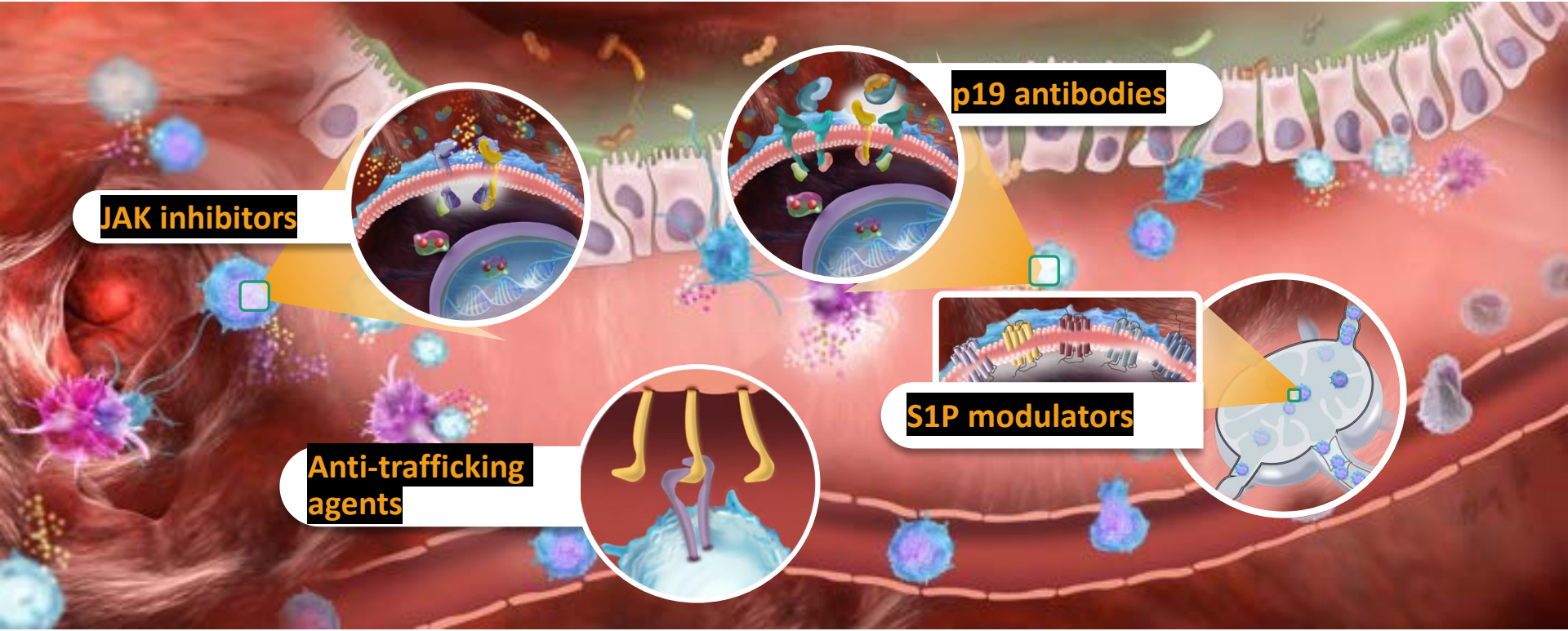


CD, Crohn's disease; CRP, C-reactive protein; FC, fecal calprotectin; IBD, inflammatory bowel disease; IOIBD, International Organization for the Study of IBD; SPIRIT, Selecting Endpoints for Disease-Modification Trials; STRIDE, Selecting Therapeutic Targets in Inflammatory Bowel Disease; UC, ulcerative colitis.

1. Peyrin-Biroulet L, et al. *Am J Gastroenterol*. 2015;110:1324–38; 2. Turner D, et al. *Gastroenterology*. 2021;160:1570–83; 3. Le Berre C, et al. *Gastroenterology*. 2021;160:1452–60.e21.

Figure adapted from Le Berre C, et al. Gastroenterology. 2021;160:1452–60.e21.

Evolving Targets in IBD



What evidence can we use to position therapies?

Drug-to-placebo studies: different exposures to medications

Real world effectiveness studies

Victory, Evolve, others

Head-to-Head Studies

Varsity, Hibiscus, Gardenia

Network meta-analyses

Advanced Therapies are Affected by Prior Exposure to Anti-TNF Therapy in CD

Clinical remission: Absolute difference versus placebo

	Anti-TNF-naïve	Anti-TNF-exposed
Adalimumab (Week 56, CHARM)[1,2]*	42.0%	31.0%
Vedolizumab (Week 52, GEMINI 2)[3,4]	22.1%	14.9%
Ustekinumab (Week 8, UNITI-1 and -2)[5,6]	20.6%	13.6%

Adalimumab, vedolizumab, and ustekinumab demonstrated **decreased efficacy in anti-TNF–exposed patients with CD**[1-3]

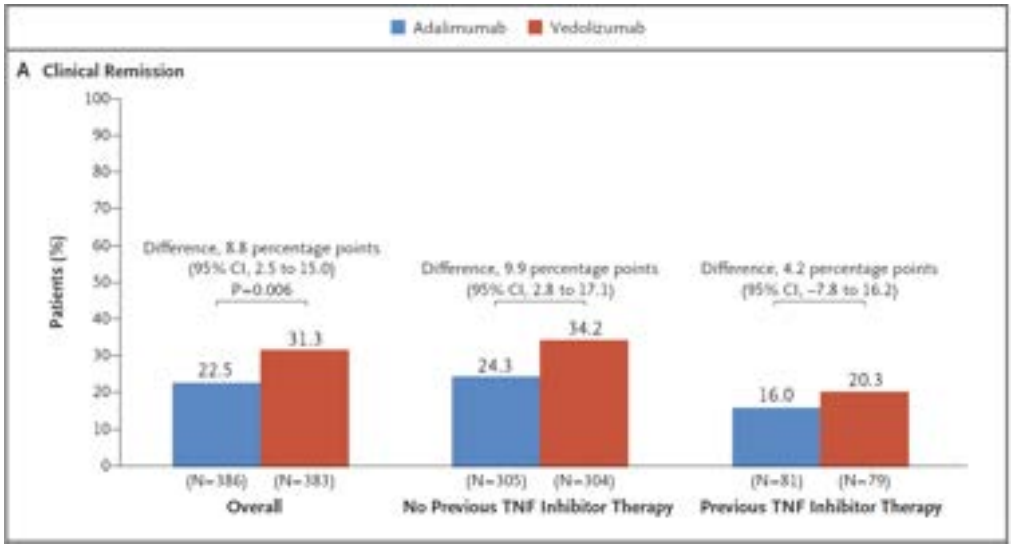
*The adalimumab 40 mg every other week dosing regimen cohort data was used.[1]

CD, Crohn's disease; CHARM , Crohn's Trial of the Fully Human Antibody Adalimumab for Remission Maintenance; TNF, tumour necrosis factor.

1. Colombel JF, et al. *Gastroenterology*. 2007;132:52–65; 2. Humira® (adalimumab) SmPC. European Medicines Agency. October 2022. Available at: https://www.ema.europa.eu/en/documents/product-information/humira-epar-product-information_en.pdf. Accessed October 2023; 3. Sands BE, et al. *Inflamm Bowel Dis*. 2017;23:97–106; 4. Entyvio® (vedolizumab) SmPC. European Medicines Agency. September 2023. Available from: https://www.ema.europa.eu/en/documents/product-information/entyvio-epar-product-information_en.pdf. Accessed October 2023; 5. Feagan BG, et al. *N Engl J Med*. 2016;375:1946–60 (supplementary appendix); 6. Stelara® (ustekinumab) SmPC. European Medicines Agency. July 2023. Available from: https://www.ema.europa.eu/en/documents/product-information/stelara-epar-product-information_en.pdf. Accessed October 2023.

VARSITY in Ulcerative Colitis

- Phase 3b, randomized, double-blind, double-dummy, active-controlled study comparing *vedolizumab* versus *adalimumab*
- Adults with moderate to severe UC failing conventional therapy
- Exposure to one prior antiTNF (not ADA) capped at 25%

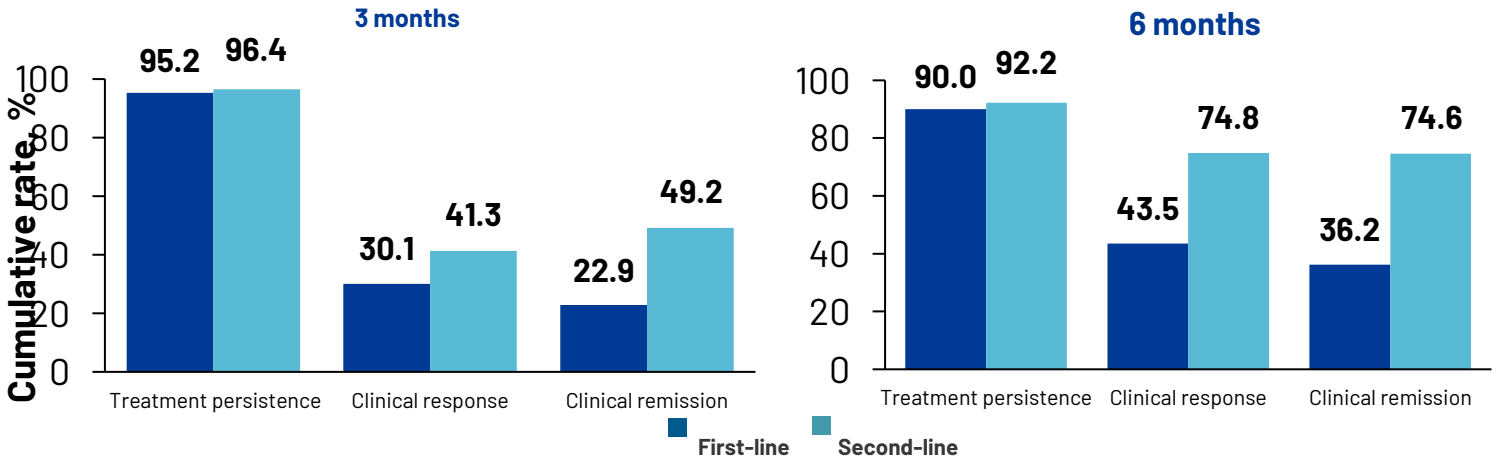


N Engl J Med. 2019 Sep 26; 381(13):1215-1226

Real-world Data Suggests that First-line VDZ may not Impact the Effectiveness of Subsequent Anti-TNFα Treatment

EVOLVE (N=1,095)

Cumulative rates of treatment persistence and clinical effectiveness in second-line cohort were similar to rates in first-line anti-TNFα cohort[1]



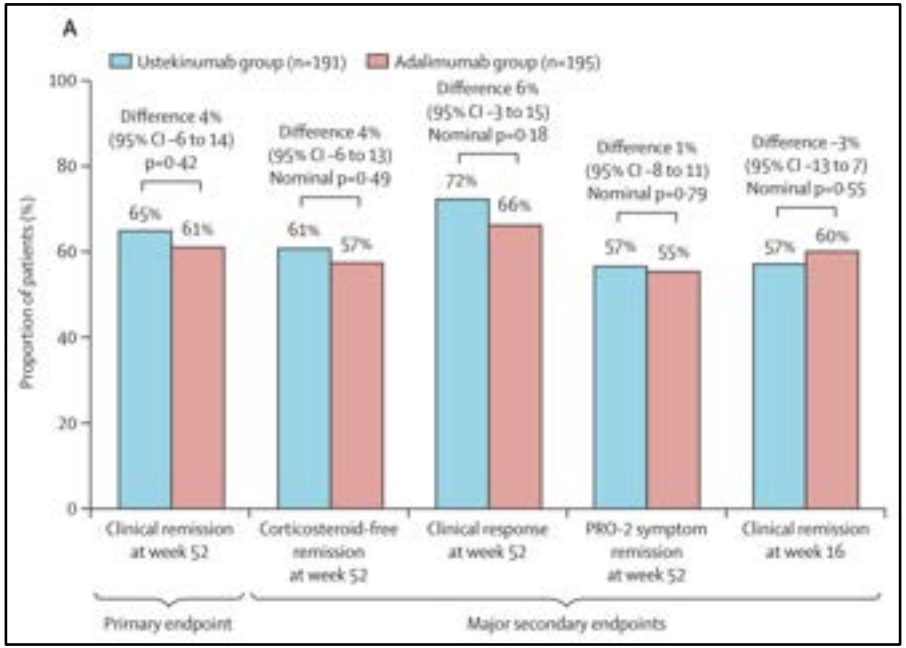
37 sites: First-line anti-TNFα (n=497).[2]

*number at risk.[1]
CD, Crohn's disease; TNFα, tumour necrosis factor alpha; VDZ, vedolizumab.

1. Bressler B, et al. *J Crohns Colitis*. 2021;15:1694–706 (supplementary appendix); 2. Bressler B, et al. *J Crohns Colitis*. 2021;15:1694–706.

SEAVUE in Crohn's Disease

- Phase 3b, randomized, double-blind, double-dummy, active-controlled study comparing *adalimumab* versus *ustekinumab*
- Adults with moderate to severe CD failing conventional therapy
- All patients were biologic-naïve



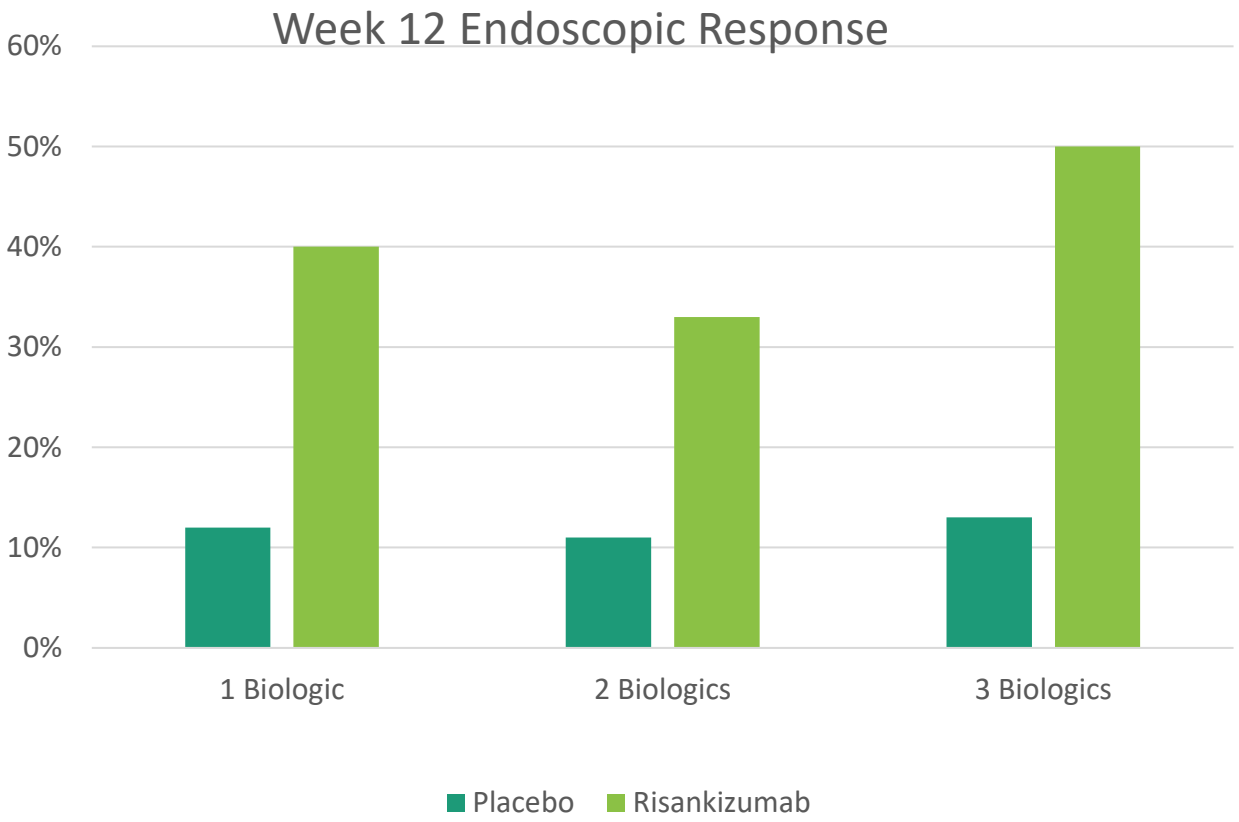
The Lancet. 2022 Jun 11; 399(10342):2200-11.

Comparative Efficacy of Agents in Anti-TNF Exposed Patients: Network Meta-Analysis of Crohn's disease Clinical Remission

Medications	Relative Effect (Odds Ratio, 95% CI)	Overall Quality of Evidence
Selected Agents vs Placebo		
Adalimumab	**3.57 (1.66-7.65)**	**Moderate (imprecision, indirectness)**
Vedolizumab	1.53 (0.77-3.06)	Low (very serious imprecision)
Ustekinumab	**2.58 (1.50-4.44)**	**Moderate (imprecision)**
Selected Agents vs Adalimumab		
Vedolizumab	0.43 (0.15-1.20)	Very low (very serious imprecision, intransitivity)
Ustekinumab	0.72 (0.28-1.85)	Very low (very serious imprecision, intransitivity)
Selected Agents vs Vedolizumab		
Ustekinumab	1.68 (0.68-4.15)	Very low (very serious imprecision, intransitivity)

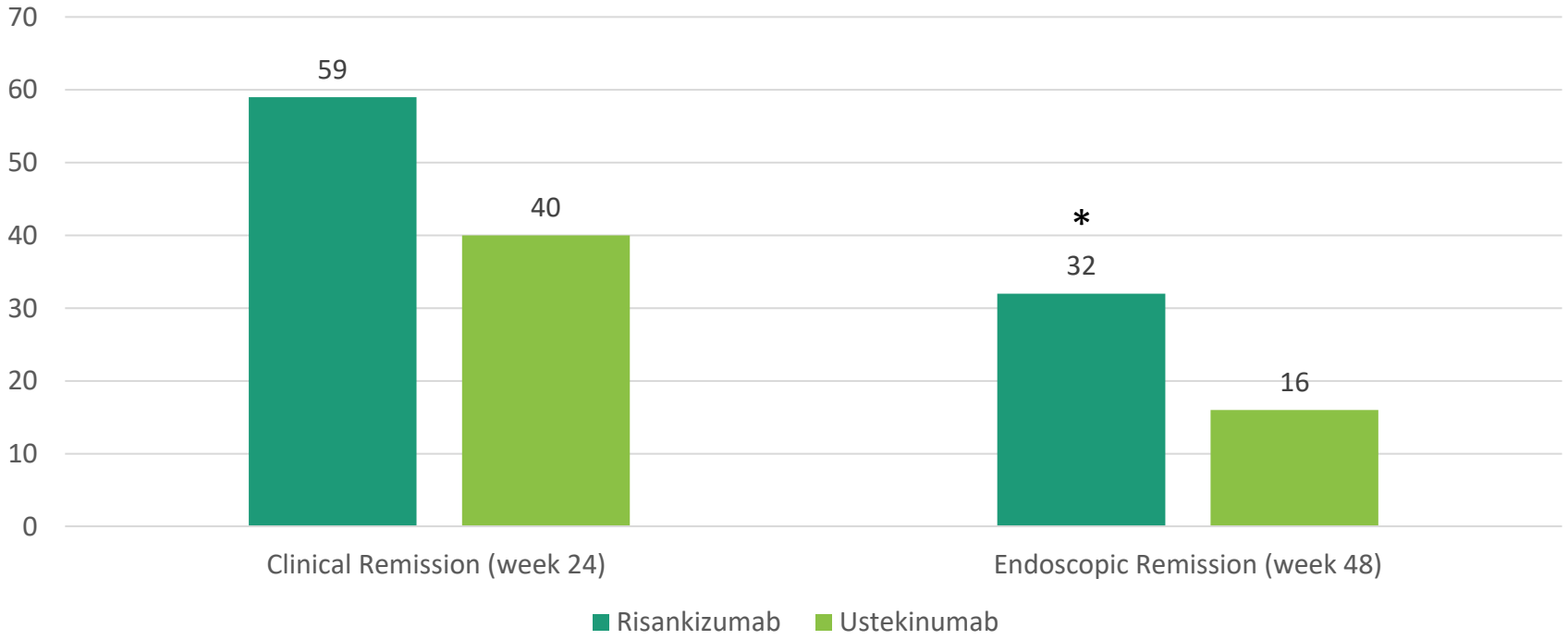
Abbreviations: CI, confidence interval; TNF, Tumor necrosis factor.
Singh S, et al. *Gastroenterology*. 2021;160:2512-2556.

Risankizumab and Biologic Exposures



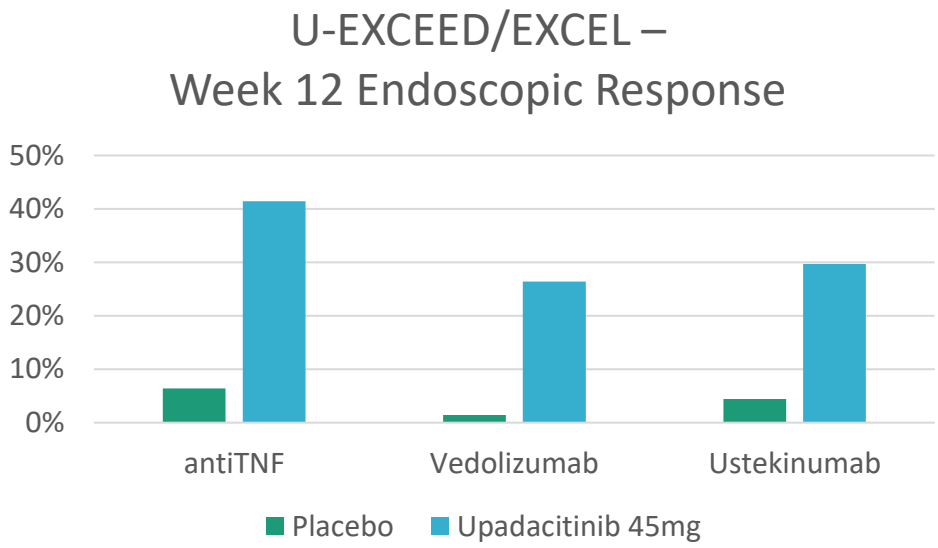
D'Haens et al. Lancet 2022

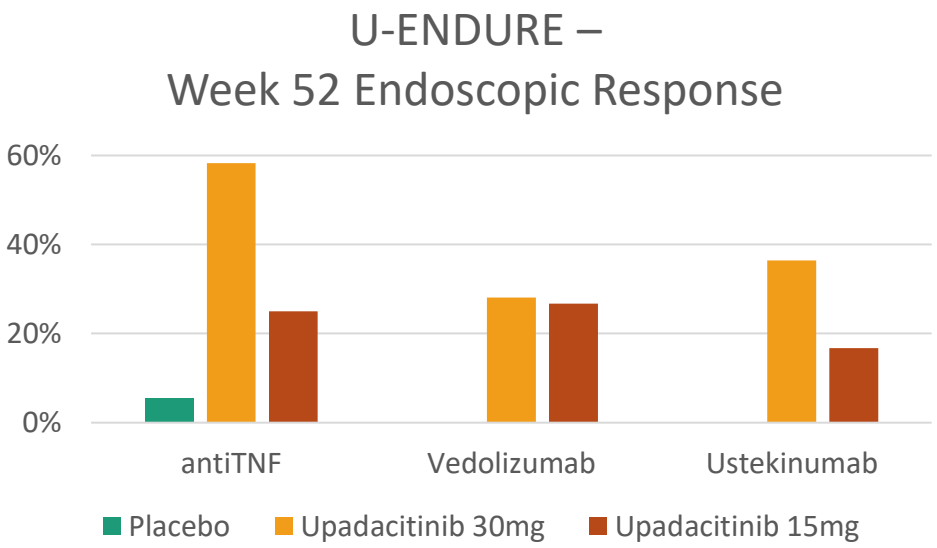
SEQUENCE, a Phase 3 head-to-head study comparing Ustekinumab to Risankizumab



Abbvie Press Release, Sep 13, 2023

Upadacitinib and 1 Biologic Exposure

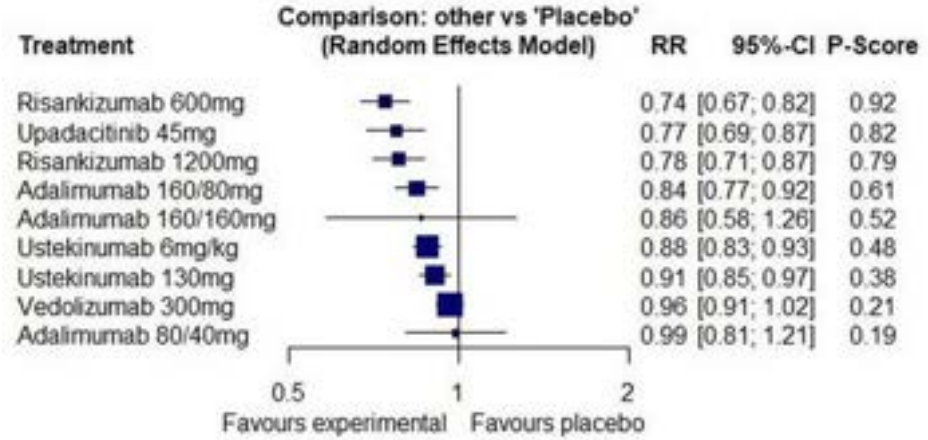




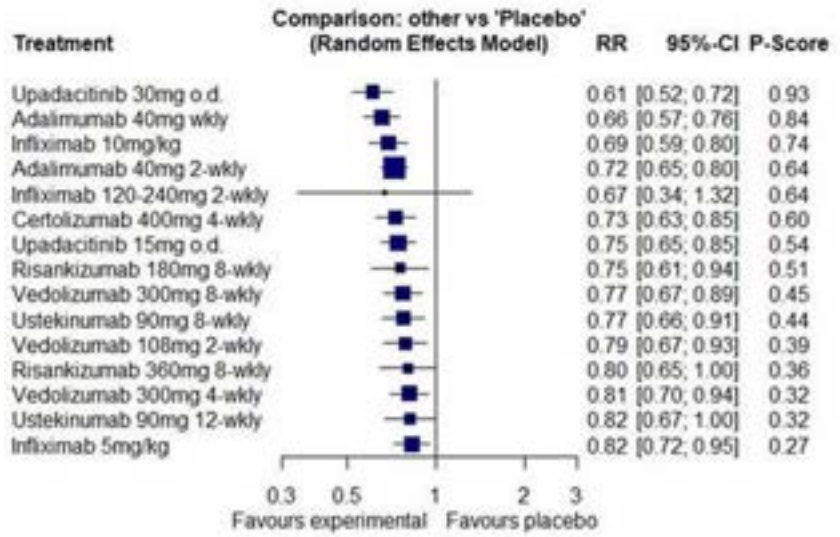
Loftus EV et al. NEJM 2023

Updated Network Meta-Analysis

Failure to Induce Clinical Remission



Relapse of Disease Activity During Maintenance



- Risankizumab ranked first for induction of clinical remission in biologic exposed
- Upadacitinib 30mg ranked first for maintenance of clinical remission in biologic exposed

Barberio B et al. Gut 2023

There are Many Additional Factors in Treatment Decision-Making

- **Patient Factors**
- **Disease Factors**
- **Treatment Factors**

What Do I Take into Account When Choosing a Medication for IBD?

Patient and disease factors:

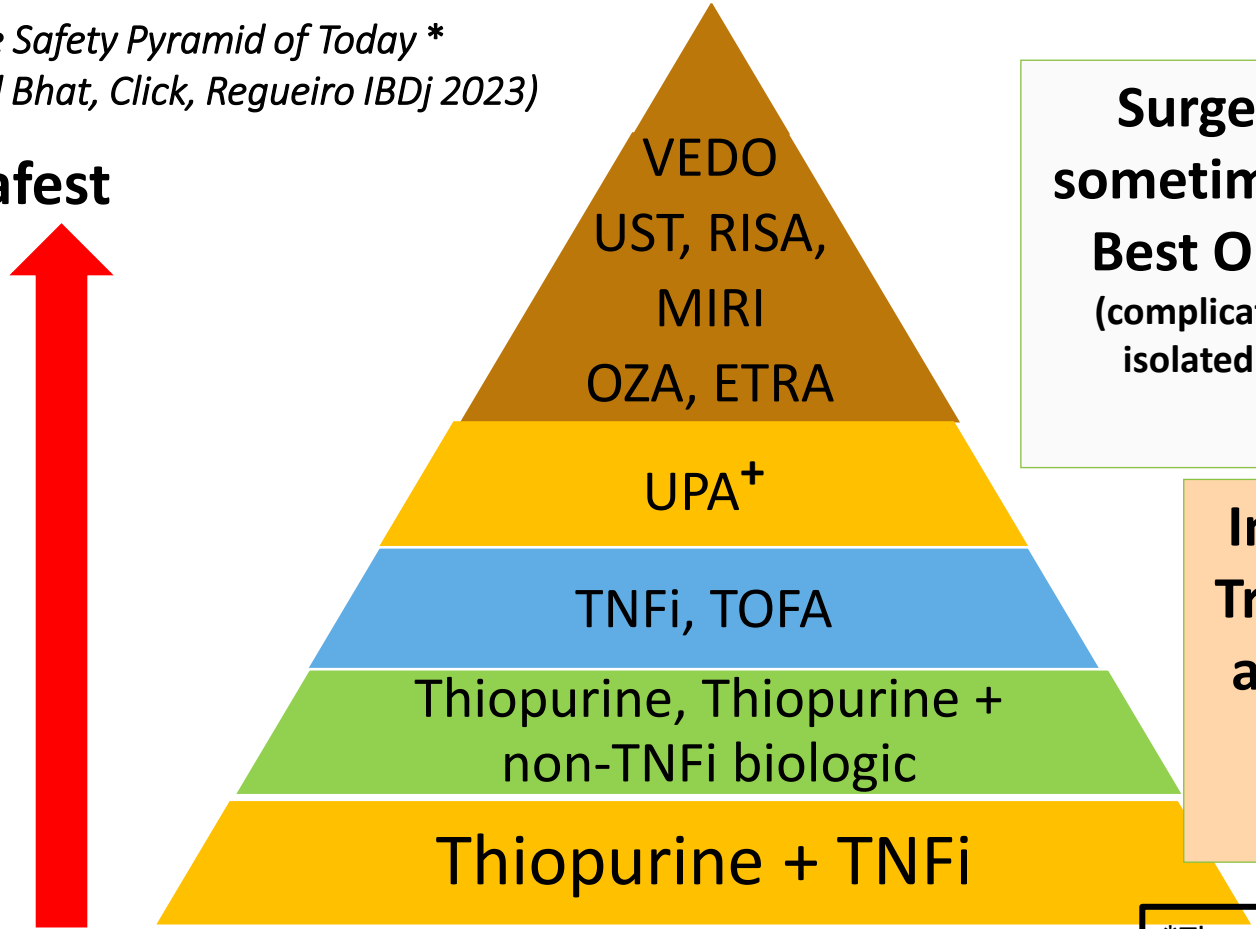
- Co-morbidities–e.g. cancer or cancer risk, infection risk
- Age, childbearing (ozanimod unclear risk, Jaki)
- EIMs
- Naïve patient versus previous biologic exposure
- Colonic extent
- Disease severity

Patient preference: IV, subq, oral

Cost and/or insurance coverage/what is available in your country

*The Safety Pyramid of Today **
(adapted Bhat, Click, Regueiro IBDj 2023)

Safest



Surgery is sometimes the Best Option
(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

Synthesizing Choices in UC Treatment

Mild | Moderate (+/- steroid-dependent) | Severe (steroid-refractory)

Naïve
(mostly equipoised, patient preference important)

Ozanimod/etrasimod
(proctitis)
(may be better than adalimumab)

Vedolizumab>adalimumab
Ustekinumab/anti-IL-23 Abs
Infliximab

Infliximab
Cyclo

Biologic-exposed

Change mechanism if did not work
Some patients will benefit from combined biologics

JAKi (tofa, upadacitinib) if failed anti-TNFs
(Avoid if CV/VTE risk factors)

Tofa/upadacitinib (JAKi) and ustekinumab/mirikizumab/Risankizumab (IL-23) similar mechanisms
Verdict out on S1P agonists and JAKi in pregnancy
I generally do not choose vedolizumab if dealing with EIMs.

Potential Treatment Sequence of Agents in CD

CD (considering magnitude of benefit for endoscopic remission/ mucosal healing)	
Anti-TNFα-naïve	**Anti-TNFα-exposed**
Risankizumab, ustekinumab, or vedolizumab	Risankizumab or ustekinumab or Upadacitinib

When looking at the long-term benefit of optimized outcomes, **biologic sequencing** of an agent should be considered for anti-TNFα-naïve and anti-TNFα exposed patients as the **treatment efficacy may be impacted**[1]

***No sequence is recommended within each category.**
Upadacitinib could also be considered as an induction and maintenance treatment in patients with moderately to severely active CD.[2,3]
CD, Crohn's disease; TNFα, tumor necrosis factor alpha.
1. Bressler B. *Therap Adv Gastroenterol*. 2023;16:17562848231159452; 2. Loftus EV Jr, et al. *N Engl J Med*. 2023;388;1966–80 3. Rinvoq® (upadacitinib) SmPC. European Medicines Agency. August 2023. Available from: https://www.ema.europa.eu/en/documents/product-information/rinvoq-epar-product-information_en.pdf. Accessed October 2023.

Synthesizing Choices in CD Treatment

Mild | Moderate | Severe or Fistulizing disease

Naïve
(mostly equipoised, patient preference important)

Adalimumab
Vedolizumab
Ustekinumab
Risankizumab

Infliximab
Ustekinumab
Risankizumab

Biologic-exposed

Depends on initial MoA
Risankizumab
Upadacitinib

JAKi (upadacitinib) if failed anti-TNFs
Works in fistulizing disease
Works quickly

What if Other Factors Drive Risk of Disease Progression in IBD?

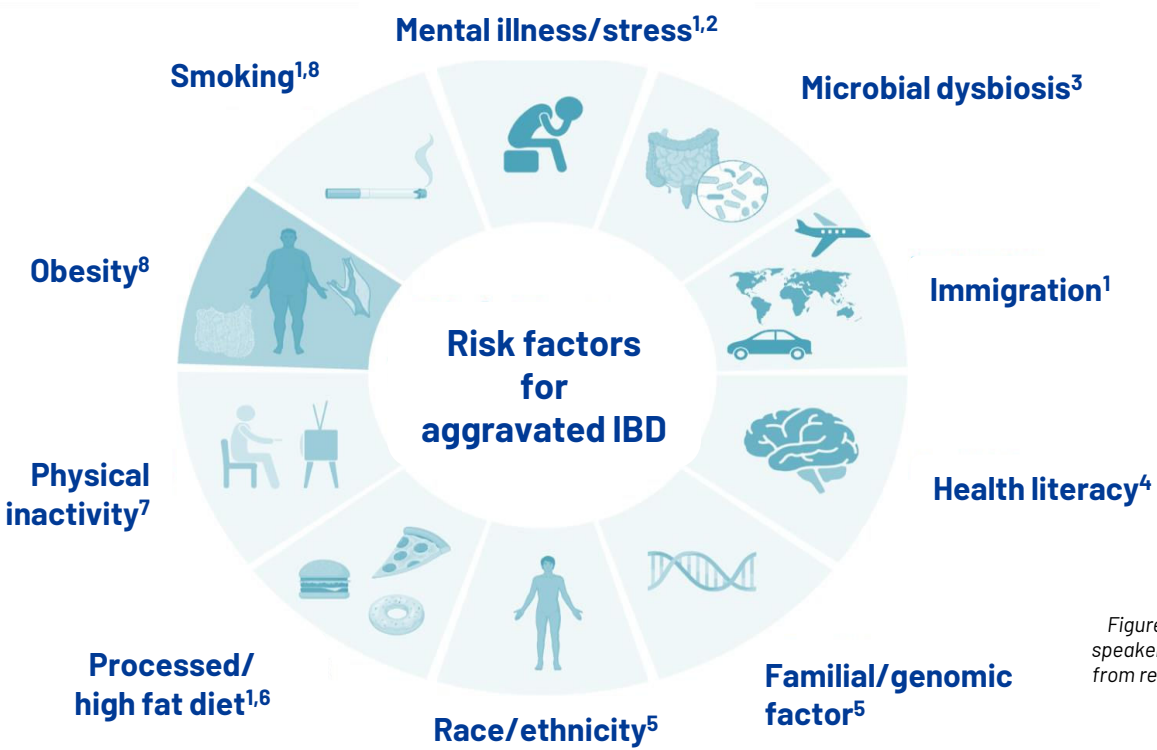


Figure created by speaker and adapted from reference data.

IBD, inflammatory bowel disease.

1. Ye Y, et al. *Int J Clin Exp Med*. 2015;8:22529-42; 2. Eugenicos MP, Ferreira NB. *Br Med Bull*. 2021;138:16–28; 3. Santana PT, et al. *Int J Mol Sci*. 2022;23:3464; 4. Tormey LT, et al. *Inflamm Bowel Dis*. 2019;25:204-212; 5. Santos MPC, et al. *Ann Gastroenterol*. 2018;31:14-23; 6.Vissers E, et al. *Front Med (Lausanne)*. 2022;9:1058373; 7. Bilski J, et al. *Biomed Res Int*. 2014;2014:429031; 8. Carreras-Torres R, et al. *Sci Rep*. 2020;10:19273.

Take home points

Consider the full picture:

- Disease severity, acuity
- Extraintestinal manifestations, fistulizing disease
- Age, pregnancy planning and comorbidities and safety

Best sequence of advanced therapies:

- First line vs second line therapy differ in efficacy
- Prior antiTNF exposure associated with reduced efficacy for vedolizumab and ustekinumab
- Exposure to other biologics may not impact efficacy of antiTNF efficacy (more data needed)
- Risankizumab and Upadacitinib with good efficacy after all biologic exposures