

Reimagining Anti-TNF Therapy in IBD: Evidence-Based Best Practices and Subcutaneous Treatment Options

David T. Rubin, MD, FACG, creator

*Joseph B. Kirsner Professor of Medicine
Chief, Section of Gastroenterology, Hepatology, and Nutrition
Director, Inflammatory Bowel Disease Center
University of Chicago*

Marla Dubinsky, MD, moderator

*Professor of Pediatrics and Medicine
Chief, Division of Pediatric Gastroenterology and Nutrition
Co-Director, Susan and Leonard Feinstein IBD Clinical Center
Co-Director, Marie and Barry Lipman IBD Preconception and
Pregnancy Planning (I-PrePP) Clinic
Mount Sinai Kravis Children's Hospital
Icahn School of Medicine, Mount Sinai, New York*

Disclosures

- **David T. Rubin, MD, FACG:** Consultant/Advisor—AbbVie, Abivax, AltruBio, Athos Therapeutics, Bristol Myers Squibb, Celltrion, Connect BioPharma, Eli Lilly, Genentech (Roche), Iterative Health, Janssen Pharmaceuticals, Johnson & Johnson, Merck, Odyssey Therapeutics, Pfizer, Sanofi, Spyre, Takeda, Vedanta Biosciences, Ventyx; Grant Support—Gastro-Intestinal Research Foundation, Helmsley Charitable Trust, NIH P30 DK42086, Takeda; Board of Trustees/Directors—Cornerstones Health
- **Marla Dubinsky, MD:** Consultant/Advisor—AbbVie, Abivax, Amgen, AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Celltrion, Eli Lilly, Genentech, Janssen, Johnson & Johnson, Merck, Novartis, Pfizer, Prometheus Laboratories, Sanofi, Spyre Therapeutics, Takeda, Target RWE, Tentarix

Learning Objectives

- Evaluate the clinical utility of TNF inhibitors in IBD, including their impact on patient outcomes and mucosal healing
- Assess the most recent clinical trial and real-world data on the safety, efficacy, and practical use of TNF inhibitors for IBD, including their use as monotherapy or in combination with an immunomodulator, with attention to newer formulations
- Implement evidence-based strategies to optimize anti-TNF therapy in IBD, emphasizing early intervention and appropriate use of TDM to maintain stable drug levels
- Consider cost-effective methods when optimizing anti-TNF therapy

The Biologic Era in Inflammatory Bowel Disease: Why TNF Inhibitors Led the Way

Anti-TNF Therapy in IBD: Tried, Tested, and Still Leading

1 Patient factors that should prompt anti-TNF as first-line advanced therapy

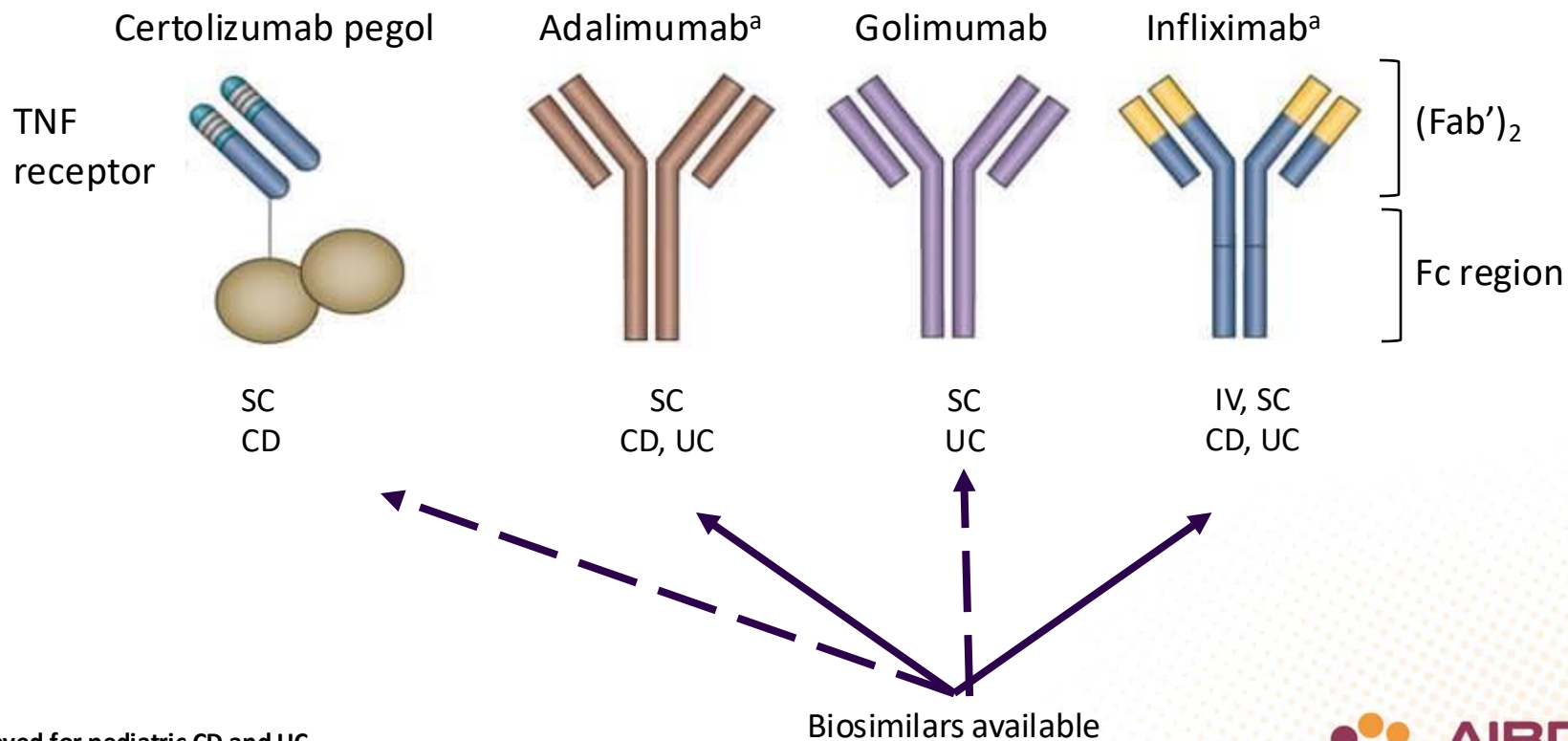
2 Anti-TNF still has the best efficacy

3 Well-known safety profile tempered by efficacy

4 New options for convenient management

5 Anti-TNFs are available and cost-effective

Anti-TNF Therapies in IBD



^aApproved for pediatric CD and UC.

CD = Crohn's disease; UC = ulcerative colitis.

Adapted from Van Vollenhoven RF. *Nat Rev Rheumatol.* 2011;7(4)205-215.

We Learned the Most about Anti-TNF Therapies!

- What a biologic therapy is
 - Immunogenicity
 - The importance of maintenance therapy
 - The concept of “top-down” treatment
 - Disease modification is possible
 - Biosimilar switches are safe and effective
 - Immune-based adverse events
- How to design improved clinical trials in IBD
 - Randomized responders
 - Ethics of access and need for long-term extension
 - The role of concomitant steroids
 - Deeper endpoints

The Right Patient for Anti-TNF: Guideline-Based Recommendations

Moderately-to-severely active UC or CD: Induction and maintenance of remission (adults and pediatrics)

Acute severe UC: Infliximab after disease refractory to IV corticosteroids

Perianal fistulizing CD: Induction and maintenance of remission

Post-operative CD to prevent recurrence

Rubin, DT, et al. *Am J Gastroenterol*. 2025;120(6):1187-1224. Hardbord M, et al. *J Crohns Colitis*. 2017;11(7):769-784. Bressler B, et al. *Gastroenterology*. 2015;148(5):1035-1058. Choi CH, et al. *Intest Res*. 2017;15(1):7-37. Wei SC, et al. *Intest Res*. 2017;15(3):266-284. Feuerstein JD, et al. *Gastroenterology*. 2020;158(5):1450-1461. Bitton A, et al. *Am J Gastroenterol*. 2012;107(2):179-194. Brown SR, et al. *Colorectal Dis*. 2018;20(Suppl 8):3-117. Sands BE, et al. *N Engl J Med*. 2004;350(9):876-885. Lichtenstein GR, et al. *Am J Gastroenterol*. 2018;113(4):481-517. Nguyen GC, et al. *Gastroenterology*. 2017;152(1):271-275.

AGA 2024 Moderate-to-Severe UC Guidelines

Adult outpatients with moderate-to-severely active UC

SUGGEST early use of advanced therapies and/or immunomodulator therapy, rather than gradual step up after failure of 5-aminosalicylates.
(Conditional recommendation, very low certainty of evidence)

RECOMMEND using any of the following, over no treatment: Infliximab, golimumab, vedolizumab, tofacitinib^a, upadacitinib^a, ustekinumab, risankizumab, guselkumab, ozanimod, and etrasimod
(Strong recommendation, moderate certainty of evidence)

SUGGEST using any of the following, over no treatment: Adalimumab, mirikizumab or filgotinib^a
(Conditional recommendation, moderate certainty of evidence)

Implementation considerations:

- Biosimilars of infliximab, adalimumab, and ustekinumab can be considered equivalent to their originator drug in their efficacy
- Subcutaneous formulations of infliximab and vedolizumab can be considered as an alternative to the respective intravenous maintenance doses for most patients
- Extended induction or dose escalation of several advanced therapies can be considered for some patients with severe disease

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^a, risankizumab, guselkumab
- **Intermediate efficacy medications:** Golimumab, ustekinumab, tofacitinib^a, filgotinib^a, mirikizumab
- **Lower efficacy medications:** Adalimumab

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

^aThe FDA label recommends the use of JAK inhibitors only in patients with prior failure or intolerance to TNF antagonists. Filgotinib is not available for use in the United States.

AGA = American Gastroenterological Association; JAK = Janus kinase.

Singh S, et al. *Gastroenterology*. 2024;167(7):1307-1343.

ACG 2025 UC Guidelines

23. In patients with moderately to severely active UC, we recommend against monotherapy with thiopurines or methotrexate for induction of remission (Strong recommendation, low quality of evidence).

28. In patients with moderately to severely active UC, we recommend anti-tumor necrosis factor (TNF) therapy using infliximab for induction of remission (Strong recommendation, high quality of evidence).

29. In patients with moderately to severely active UC, we recommend anti-TNF therapy using adalimumab or golimumab for induction of remission (Strong recommendation, moderate quality of evidence).

33. When infliximab is used as induction therapy for patients with moderately to severely active UC, we recommend combination therapy with a thiopurine (Strong recommendation, moderate quality of evidence for azathioprine).

ECCO 2024 Guidelines for CD Therapy Positioning

	Induction	Maintenance	Perianal Disease	Peripheral Spondylo-arthritis	Axial Spondylo-arthritis	Pregnancy	>65 years
Recommended	i	i	ii				
Can be considered	iv			iv	iv	iv	iv
Not recommended						v	v
Insufficient evidence							
Systemic corticosteroids	iv			iv	iv	iv	iv
Enteral release corticosteroids						v	v
Enteral nutrition							
Thiopurines monotherapy						vi	vii
Methotrexate							
Infliximab							
Adalimumab							
Certolizumab							
Vedolizumab							
Ustekinumab							
Risankizumab				viii	ix		
Upadacitinib			x	xi	xii		xiii

ACG 2025 CD Guidelines

12. In the absence of immunomodulator or biologic treatment, corticosteroid dependency and/or resistance occurs in up to half of patients.

15. In CD, the 5-year rate of symptomatic postoperative recurrence is ~50%.

3. We suggest against requiring failure of conventional therapy before initiation of advanced therapy for the management of CD (conditional recommendation, low level of evidence).

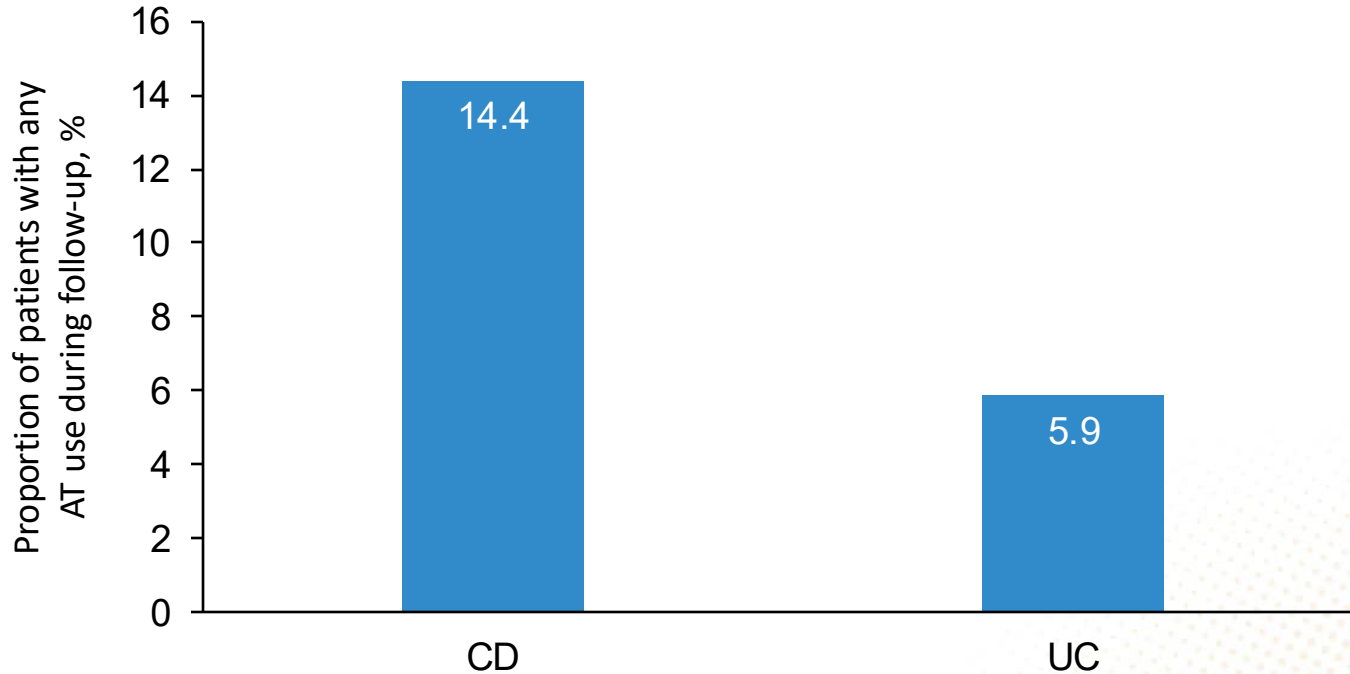
12. We recommend anti-TNF agents (intravenous infliximab, subcutaneous adalimumab, subcutaneous certolizumab pegol) for induction and maintenance of remission for moderately to severely active CD (strong recommendation, moderate level of evidence).

13. We recommend combination therapy of intravenous infliximab with immunomodulators (thiopurines) as compared with treatment with either immunomodulators alone or intravenous infliximab alone in patients with CD who are naive to those agents (strong recommendation, moderate level of evidence).

14. We recommend subcutaneous infliximab as an option for maintenance of remission in patients with moderately to severely active CD who respond to intravenous induction with infliximab (strong recommendation, moderate level of evidence).

Optimizing Outcomes with TNF Inhibitors: Challenges and Opportunities for Advancing Clinical Care of Patients with IBD

Advanced Treatment Uptake Is Low within the First Few Years of IBD Diagnosis



AT = advanced treatment (infliximab, adalimumab, certolizumab, golimumab, ustekinumab, vedolizumab, tofacitinib, natalizumab, and ozanimod)

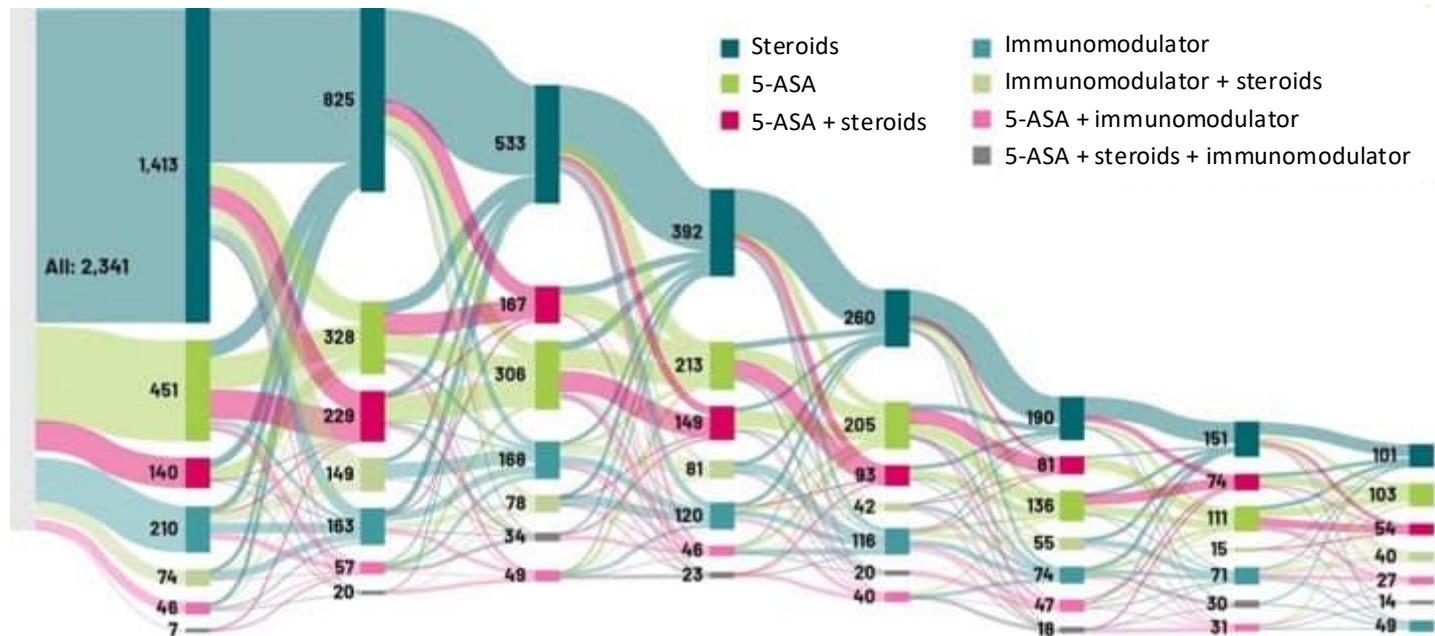
Siegel CA, et al. *Crohn's Colitis* 360. 2024;6(3):otae040.

Few Patients with Newly Diagnosed CD Initiated with Advanced Therapy First-Line, Despite Updated Recommendations

US Merative MarketScan research databases in new CD diagnoses, 2017-2021 (N=1739 patients with CD)

From diagnosis, only 14.4% of patients with CD received any advanced therapy during the mean follow-up period of 2.3 years.

13.3% of patients with CD cycled through 3 MoAs before advanced therapy initiation.

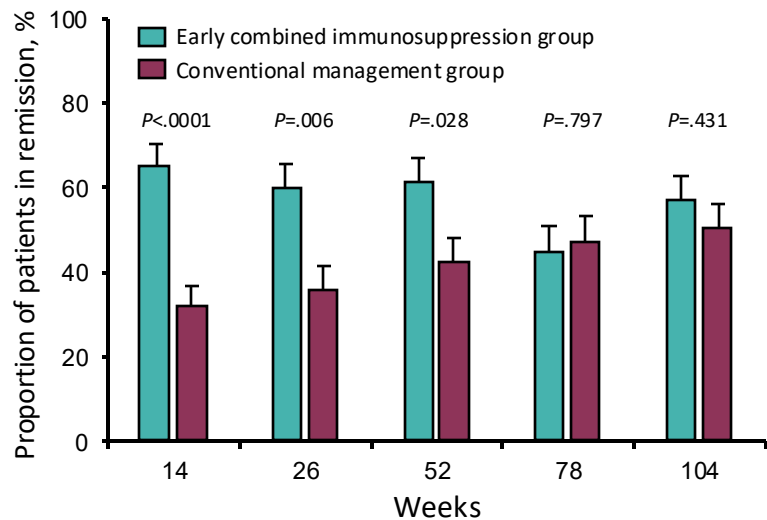
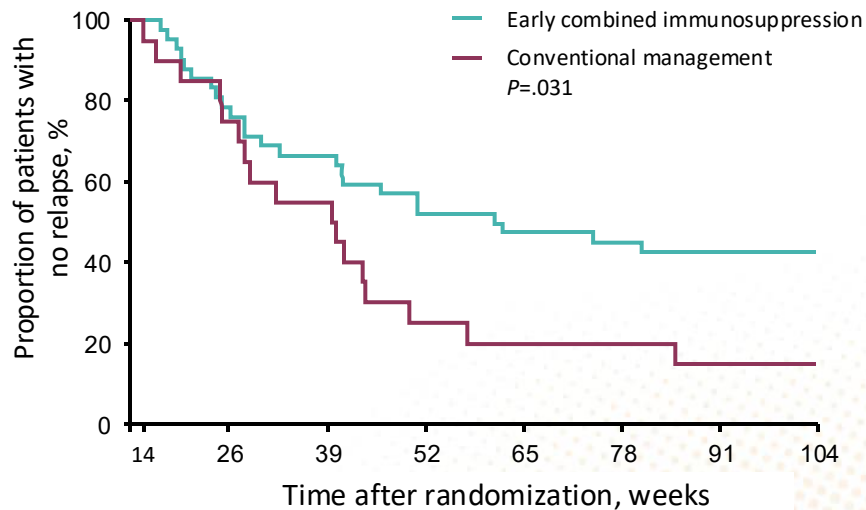


5-ASA = 5-aminosalicylate; MoA = mechanism of action.
Siegel CA, et al. *Crohn's Colitis* 360. 2024;6(3):otae040.

Timing Is Key with Anti-TNF

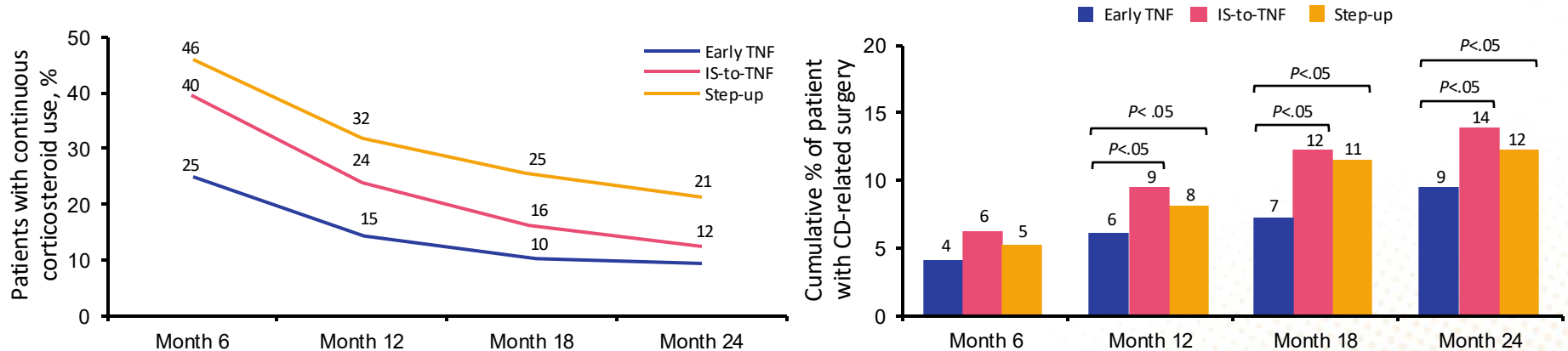
Early Combined Immunosuppression or Conventional Management in Patients with Newly Diagnosed CD (Step-Up/Top-Down)

- Median time from diagnosis to enrollment: 2 and 2.5 weeks
- An open randomized trial



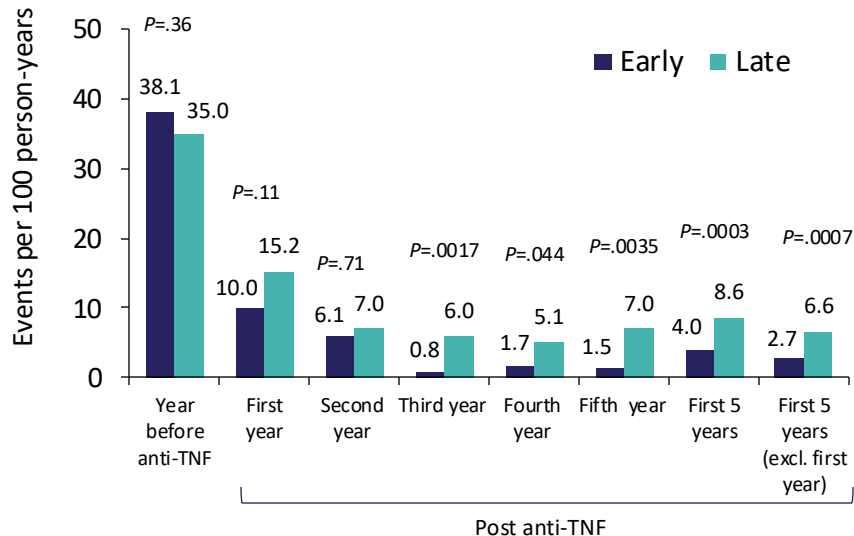
Earlier Use of Anti-TNF Biologic Therapy in CD Has Better Outcomes: Real-World Data

- Claims data assessment
- >3700 patients, all of whom received anti-TNF at some point



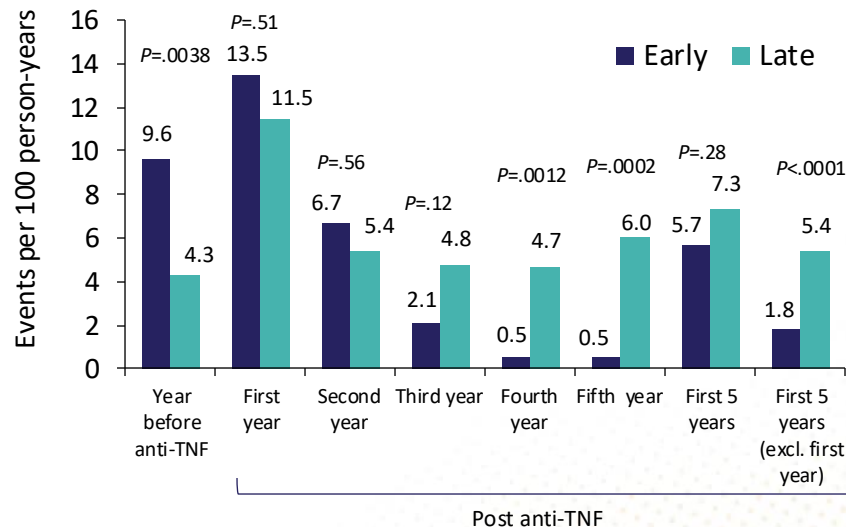
Early Anti-TNF Improves Outcomes

Total IBD-Related Hospitalizations:
Crohn's Disease



Early (n)	247	211	176	152	120	120	120
Late (n)	495	445	396	353	308	308	308

IBD-Related Surgeries:
Crohn's Disease

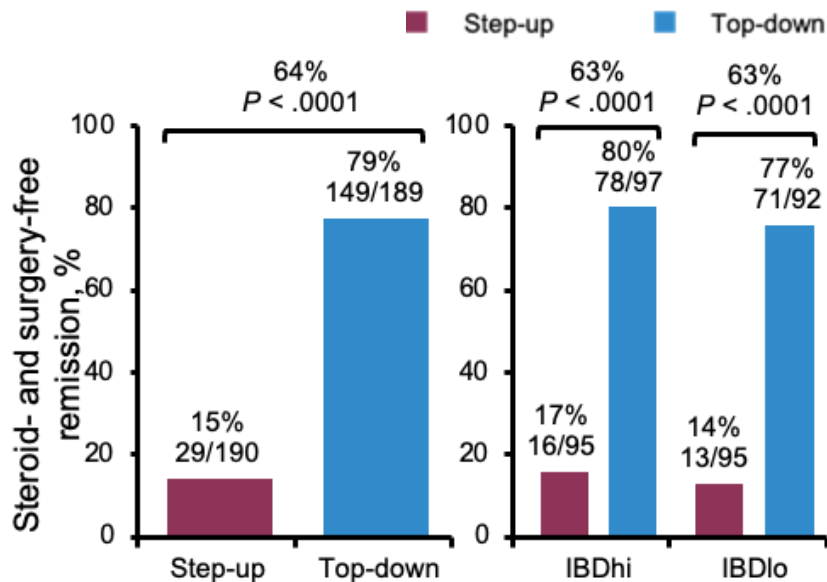


Early (n)	247	211	176	152	120	120	120
Late (n)	495	445	396	353	308	308	308

PROFILE Study: Early Therapy Improves Outcomes

Median time from diagnosis to enrollment (days; min-max): Step-up group (14; 0-191); top-down group (9; 0-168)

Sustained Steroid-Free and
Surgery-Free Remission: Primary Endpoint

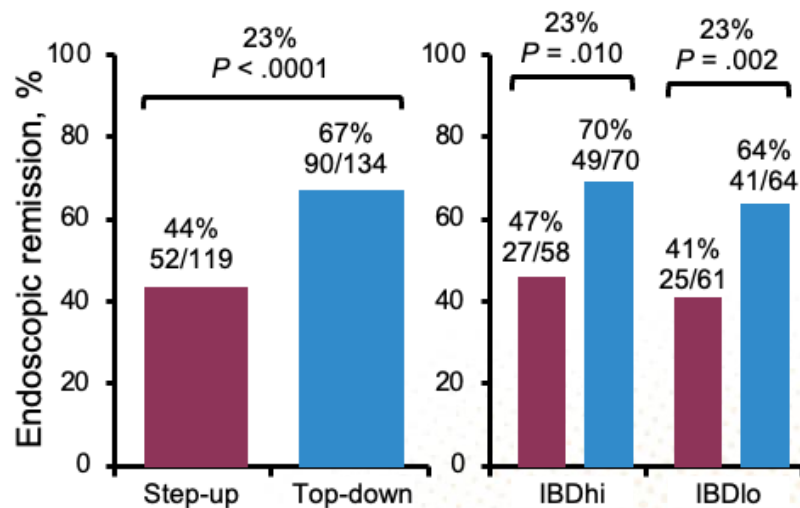


Week 48 Endoscopic Remission (No Ulcers)

Central read + local read

Central read only

Statistical test not performed as
not part of a *priori* analysis plan



Early infliximab/IMM treatment achieves nearly 80% remission rate.

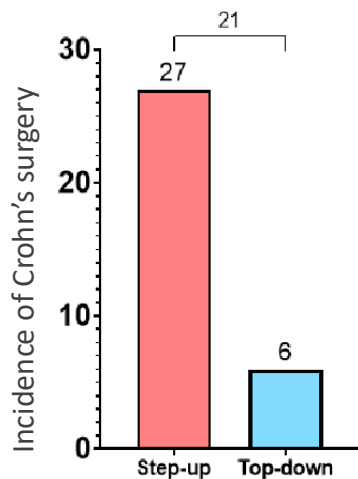
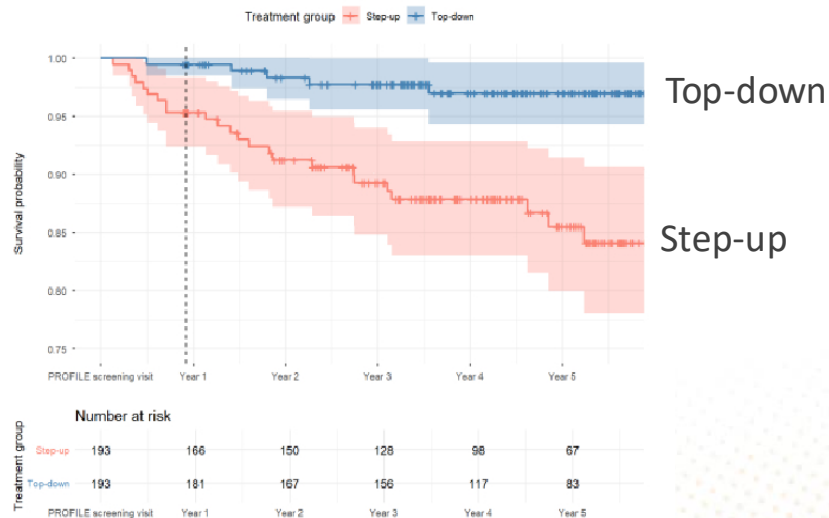
IMM = immunomodulator.

Noor NM, et al. *Lancet Gastroenterol Hepatol.* 2024;9(5):415-427.

PROFILE Study: 4-Year Follow-Up Data

Top-down therapy in Crohn's effective 4 years out and may modify longer-term disease course

Odds ratio = 5.00; 95% CI=2.02-12.43; $p<0.001$



ECCO 2024 CD Guideline: Critical Importance of Early Effective Therapy

ECCO 2020 CD Treatment Guideline

Monoclonal antibodies

Recommendation 1.5. ECCO CD Treatment GL [2020]

“We recommend the use of TNF inhibitors [infliximab, adalimumab, and certolizumab pegol] to induce remission in patients with moderate-to-severe CD who have not responded to conventional therapy [strong recommendation, moderate-quality evidence].”

...

“Furthermore, anti-TNF agents might be more effective if introduced earlier [in the first 2 years] in the disease course, although these results are based on post-hoc analyses from clinical trials.”



ECCO 2024 CD Treatment Guideline

3.10.2. The role of ‘treat-to-target’ and early treatment in the management of CD

“Regardless of the monitoring strategy chosen, it is increasingly clear that early effective treatment should be a focus of management in CD, with emphasis on avoidance of diagnostic delays and any delays in initiation of treatment.”

...

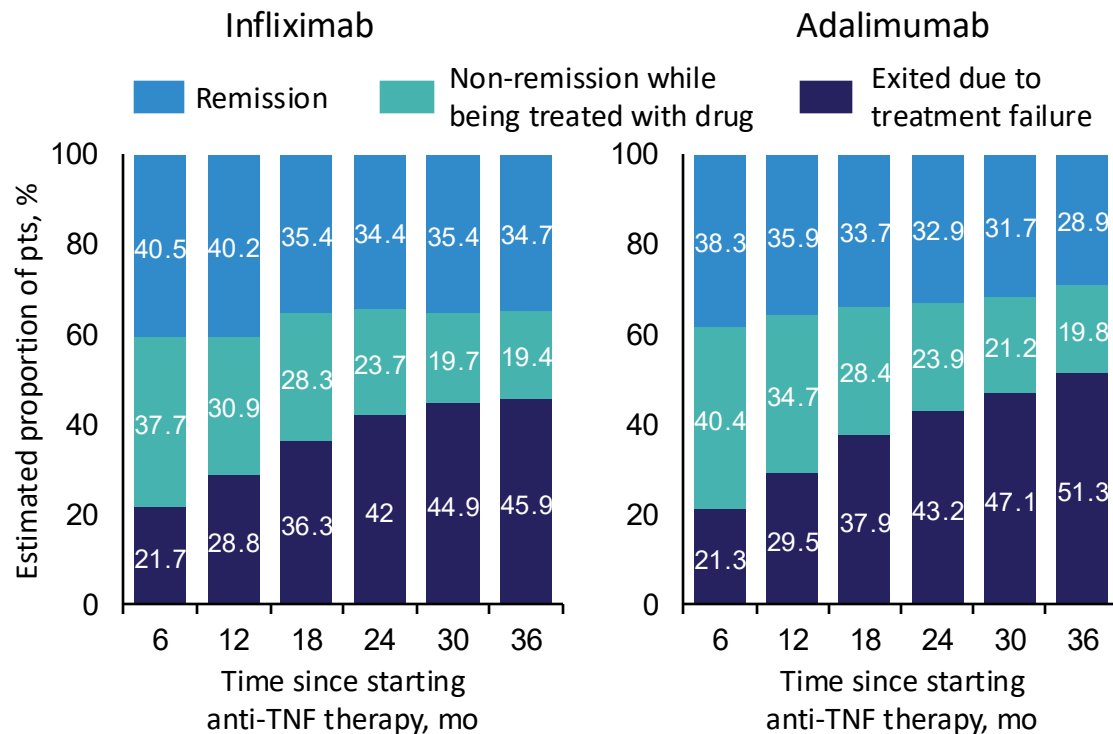
“Previous trials have hinted at the effectiveness of such an approach, and the recently reported UK PROFILE trial provides important evidence in favor of early aggressive treatment of CD.”

GL = guideline.

Torres J, et al. *J Crohns Colitis*. 2020;14(1):4-22. Gordon H, et al. *J Crohns Colitis*. 2024;18(10):1531-1555.

Dosing Is Essential with Anti-TNF

PANTS: 3-Year Follow-Up—Only Around 1/3 of Patients Were in Remission at the End of 3 Years (after Excluding PNR)



- Most LOR in first year
- Higher drug concentrations in first year of treatment may lead to better long-term outcomes
 - Early TDM
 - Combination IMM

LOR = loss of response; PNR = primary non-response; TDM = therapeutic drug monitoring.
Chanchlani N, et al. *Lancet Gastroenterol Hepatol*. 2024;9(6):521-538.

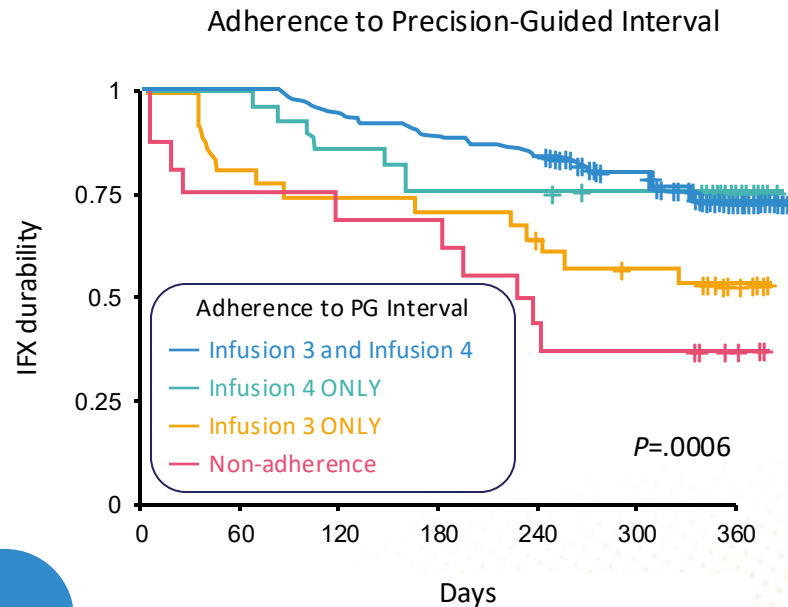
Impact of Early Proactive Precision-Guided Dosing

Week 52 outcomes, PRECISION IFX (adult and pediatric patients with IBD)

- 68% of protocol patients were still on IFX
- 97% were in CS-free remission
- Only 4% received standard maintenance dosing when continuing to target 10 $\mu\text{g/mL}$

Standard IFX dosing: 5 mg/kg x Q8W

Timing infusion 4 to achieve $\geq 10 \mu\text{g/mL}$
is key to long-term outcomes



Meta-Analysis: Proactive TDM vs SOC or Reactive TDM

Proactive TDM is better than SOC

- Treatment failure: RR 0.64 (95% CI 0.48-0.85, $P < .01$)
- Clinical remission: RR 1.07 (0.97-1.26)
- Endoscopic remission: RR 1.19 (0.93-1.53)
- Need for hospitalization: RR 0.64 (0.4-1.0)
- Surgical intervention: RR 0.51 (0.25-1.02)

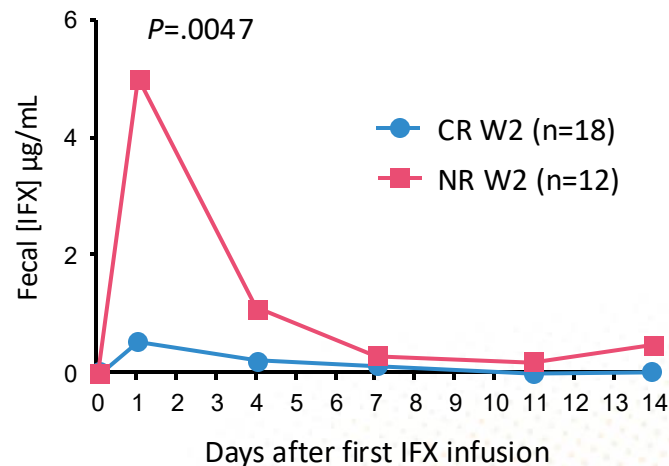
Proactive TDM is better than reactive TDM

- Treatment failure: RR 0.46 (0.21-0.98, $P = .04$)
- Need for hospitalization: RR 0.33 (0.21-0.54, $P < .01$)

Understand the Pharmacokinetics and Pharmacodynamics of Monoclonal Antibodies

	Drug Levels (Exposure)
Drug-related	↑ ↓
Presence of ADAs	↓
Concomitant use of immunomodulators	↑
High-baseline TNF- α	↓
Low albumin	↓
High-baseline CRP	↓
Increased BMI	↓
Male sex	↓

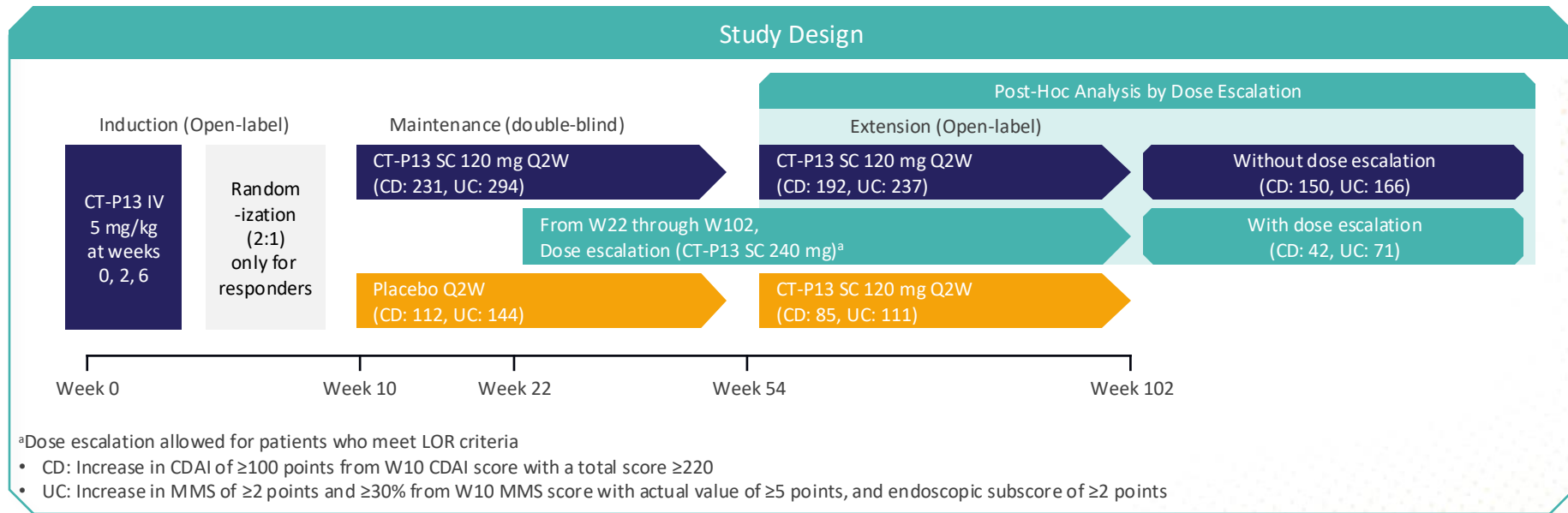
Loss of Infliximab into Feces Is Associated with Lack of Response to Therapy in Patients with Severe UC



Maintaining stable therapeutic serum levels of anti-TNF α during maintenance therapy minimizes the risk of ADAs and enhances long-term treatment efficacy.

ADAs = anti-drug antibodies; BMI = body mass index; CR = clinical response; CRP = C-reactive protein; NR = non-response.
 Ordas I, et al. *Clin Pharmacol Ther.* 2012;91(4):635-646. Brandse JF, et al. *Gastroenterology.* 2015;149(2):350-355.e2.
 Brandse JF, et al. *Clin Gastroenterol Hepatol.* 2016;14(2):251-258.e1-e2.

LIBERTY (IFX SC) Study Design

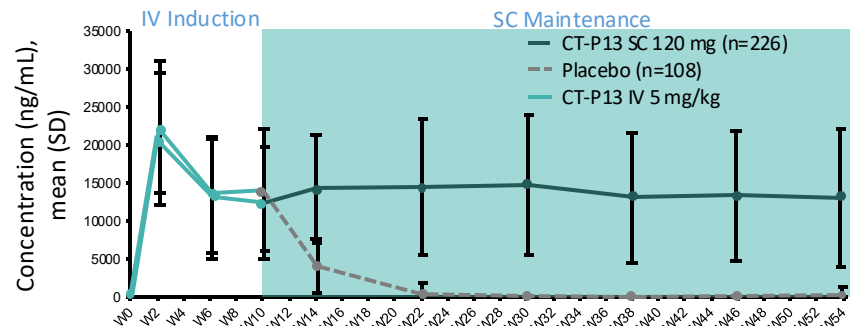


Dose Escalation Summary	CD (n=192)	UC (n=237)
Proportion of patients with DE prior to week 102, n (%)	42 (21.9%)	71 (30.0%)

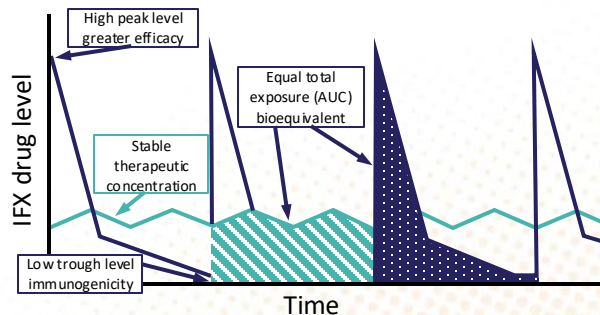
SC Infliximab for Maintenance Is Effective in UC and CD: LIBERTY-CD and LIBERTY-UC

W54 efficacy in CD, n (%)	SC IFX CD n=231	Placebo CD n=112	P-value
Clinical remission	144 (62.3%)	32 (32.1%)	<.0001
Endoscopic response	118 (51.1%)	20 (17.9%)	<.0001
Endoscopic remission	80 (34.6%)	12 (10.7%)	<.0001
Corticosteroid-free remission	39/98 (39.8%)	10/44 (22.7%)	.0434

W54 efficacy in UC, n (%)	SC IFX UC n=294	Placebo UC n=144	P-value
Clinical remission	127 (43.2%)	30 (20.8%)	<.0001
Clinical response	158 (53.7%)	45 (31.3%)	<.0001
Endoscopic-histologic mucosal improvement	105 (35.7%)	24 (16.7%)	<.0001
Corticosteroid-free remission	44/120 (36.7%)	11/61 (18%)	.0127



Proposed Theoretical Pharmacokinetic Advantages and Disadvantages between IV and SC Infliximab

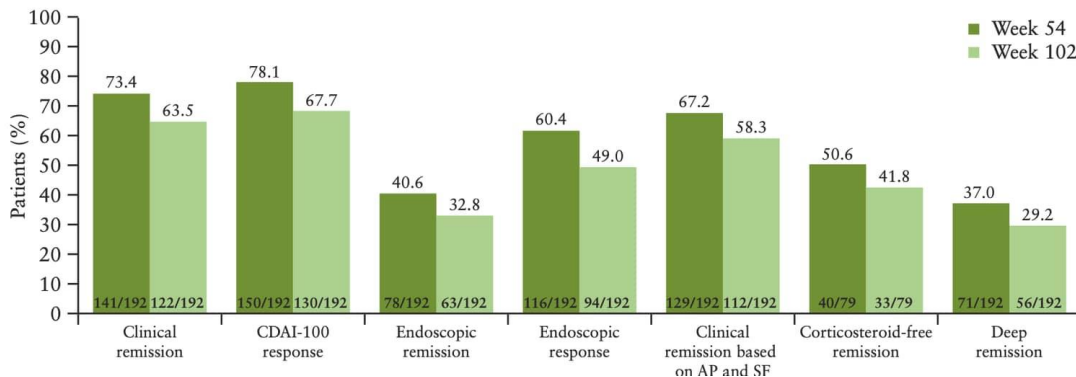


Will this PK/PD model have less immunogenicity and loss of response?

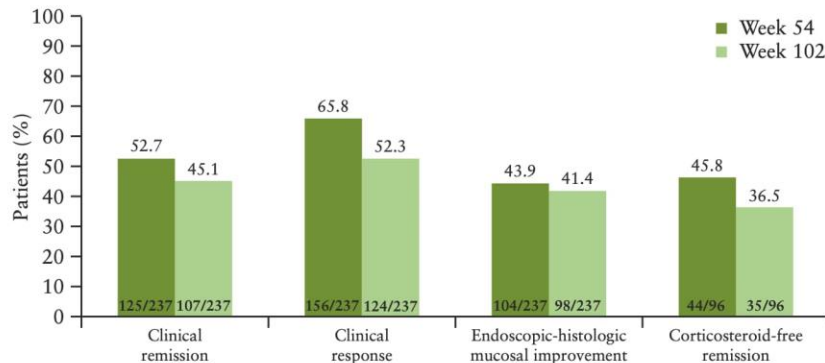
AUC = area under the curve; PD = pharmacodynamics; PK = pharmacokinetics; SD = standard deviation.
Hanauer SB, et al. *Gastroenterology*. 2024;167(5):919-933. Little RD, et al. *J Clin Med*. 2022;11(20):6173.

LIBERTY-CD and LIBERTY-UC: 2-Year Efficacy Data

LIBERTY-CD: Proportion of Patients Achieving Efficacy Endpoints



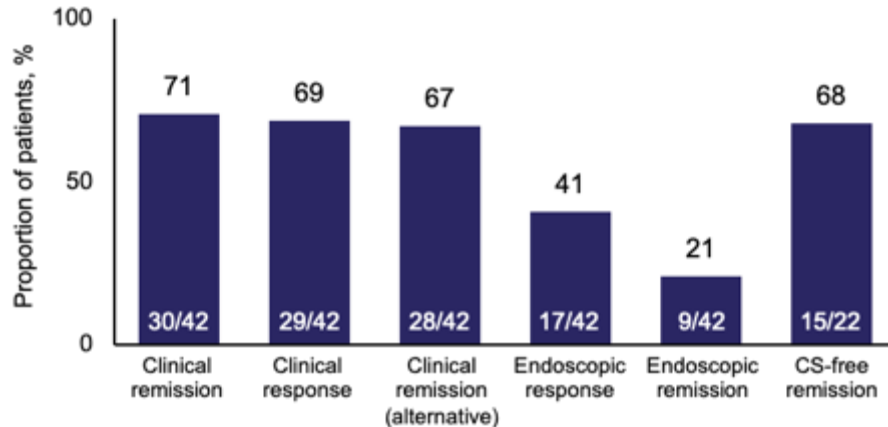
LIBERTY-UC: Proportion of Patients Achieving Efficacy Endpoints



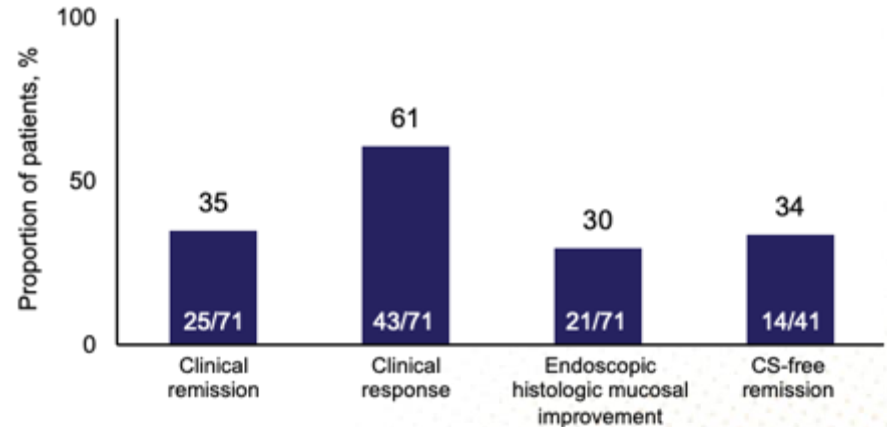
SES-CD = simple endoscopic score for CD.
Colombel JF, et al. *J Crohns Colitis*. 2025;19(6):jjaf060.

LIBERTY (IFX SC): Efficacy at Week 102 in Patients with Dose Escalation

CD (n = 42)

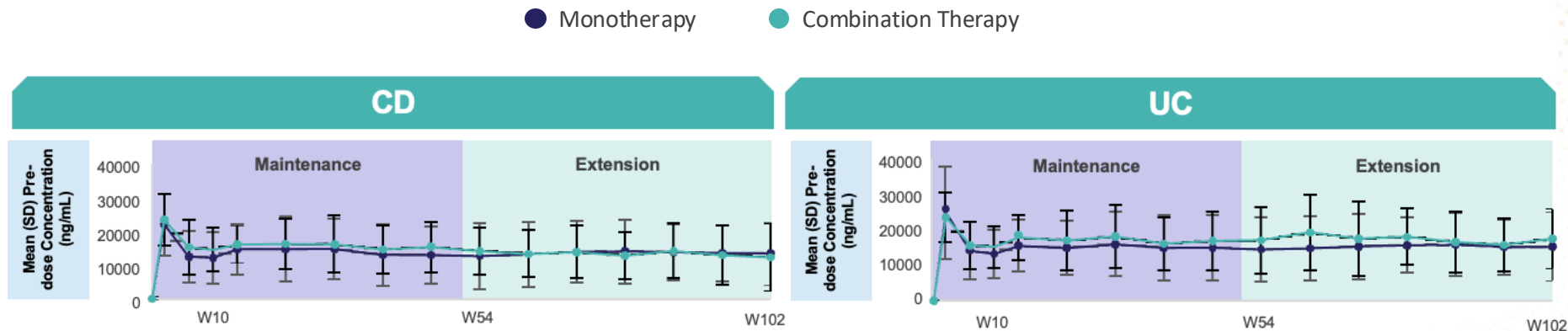


UC (n = 71)



SC infliximab maintained clinical remission rates up to 2 years, and patients who required dose escalation regained response.

Immunosuppressant Use Post-Hoc Analysis of LIBERTY (IFX SC): Pharmacokinetics

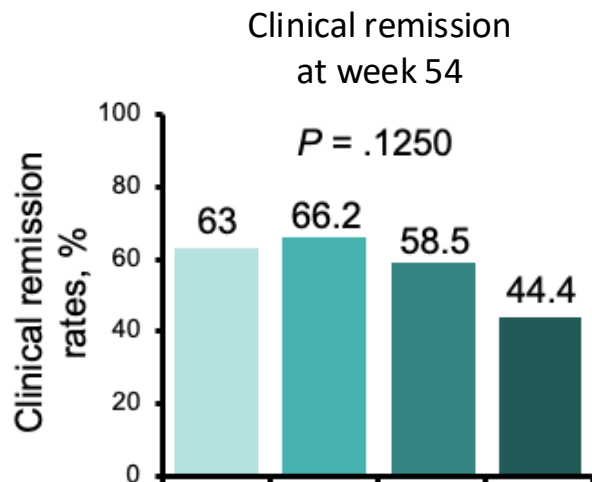
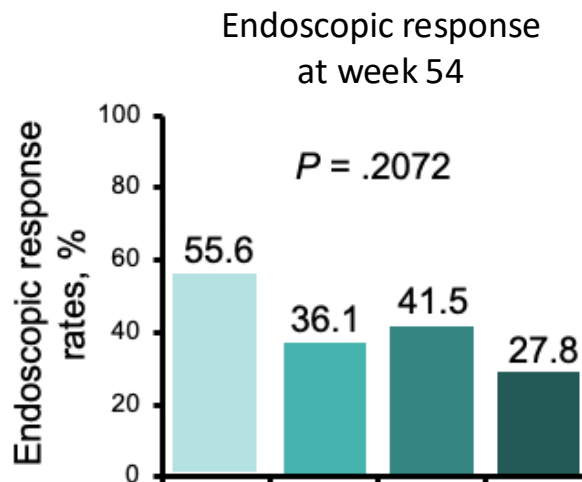
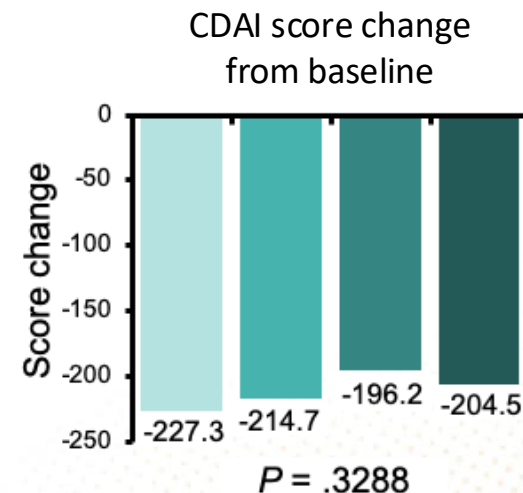


Clinical efficacy was generally similar between monotherapy and combination therapy, although combination therapy was associated with higher drug levels and lower rates of antidrug antibody formation.



LIBERTY-CD Post-Hoc Analysis: Impact of BMI on Clinical Outcomes and Drug Levels with Maintenance SC IFX

Underweight (n=27) Normal (n=133) Overweight (n=53) Obese (n=18)



IQR = interquartile range; TLI = trough level of infliximab.

Yarur A, et al. Presented at: Digestive Disease Week (DDW); 2024. Su1755.



REMSWITCH: Prediction of Long-Term Relapse after Switching from IV to SC IFX

No impact on the risk of relapse

- Weight/BMI
- Montreal classification
- Clinical activity at baseline
- CRP at baseline
- Concomitant immunosuppressive therapy
- Switching from IV to SC IFX appears to be feasible, safe, and effective
- Caution when switching patients on 10 mg/kg Q6W or more
- Monitor closely

Parameters	P-values	OR	95% CI
Fecal calprotectin level >250 µg/g at baseline	.097	3.31	0.803-13.660
IV maintenance regimen 10 mg/kg/4 weeks	<.0001	61.032	6.137-606.957
IV maintenance regimen 10 mg/kg/6 weeks	.039	4.684	1.085-20.216
IV maintenance regimen 10 mg/kg/8 weeks	.55	1.507	0.392-5.791
IV maintenance regimen 5 mg/kg/8 weeks	Ref	Ref	Ref

OR = odds ratio; CI = confidence interval; Ref = reference.
Buisson A, et al. *Clin Gastroenterol Hepatol*. 2023;21(9):2338-2346.e3.

Real-World SC IFX Effective at Inducing and Maintaining Remission in Patients with Perianal CD, Similar to IV IFX



Methods

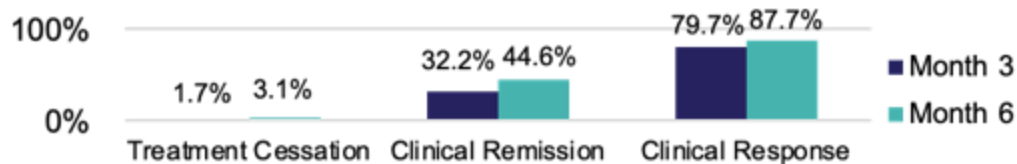
- Multicenter retrospective cohort from GETAID
- Group 1 = active perianal CD in the 6 months prior to SC switch
- Group 2 = inactive perianal CD for >6 months at time of switch but history of seton
- Clinical remission at 6 months = absence of anal ulcers and absence of draining fistula

Results: Group 1

- Active perianal CD (n=66)
- Median f/u: 50.4 weeks
- 44.6% clinical remission at 6M; 86.9% response
- 20% dose optimized (IFX >20 µg/mL)
- 72.4% MRI response; 26.5% seton removed
- Remission inversely linked to BMI, drainage, prior biologic use

Results: Group 2

- Quiescent perianal CD (n=117)
- Median f/u: 53.4 weeks
- Recurrence-free survival: 98% (3M), 92% (12M)
- 20% dose-optimized; no ADA
- 7 recurrences; 4 needed surgery



Conclusions

- SC infliximab is effective and safe for the management of active perianal CD and for maintaining remission in inactive perianal disease
- Comparable outcomes with IV infliximab

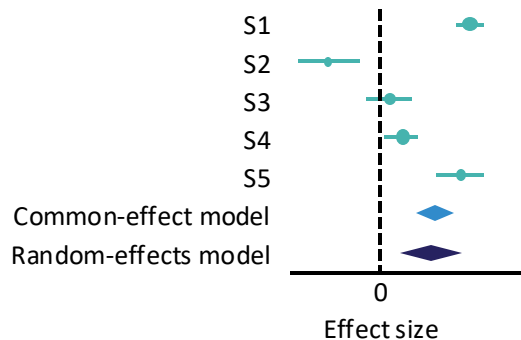
Evidence-Based Clinical and Patient Considerations When Deciding on a Strategy

Fundamental Principles in the Approach to Positioning and Sequencing of IBD Therapies

- Naïve vs exposed
- Type of treatment comparisons
- Within class vs out of class
- Need for speed
- Disease location
- Disease duration
- It's all about the biology
- Thinking outside the gut

Types of Evidence

Meta-Analysis



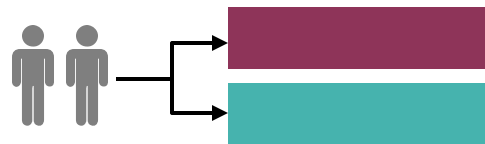
Integrates findings from many individual studies (often RCTs), applying objective statistical formulas

Real-World Data



Routinely collects data on patient health status from many sources (eg, registries), often using propensity score-matched analysis for adequate comparisons

Head-to-Head Trial



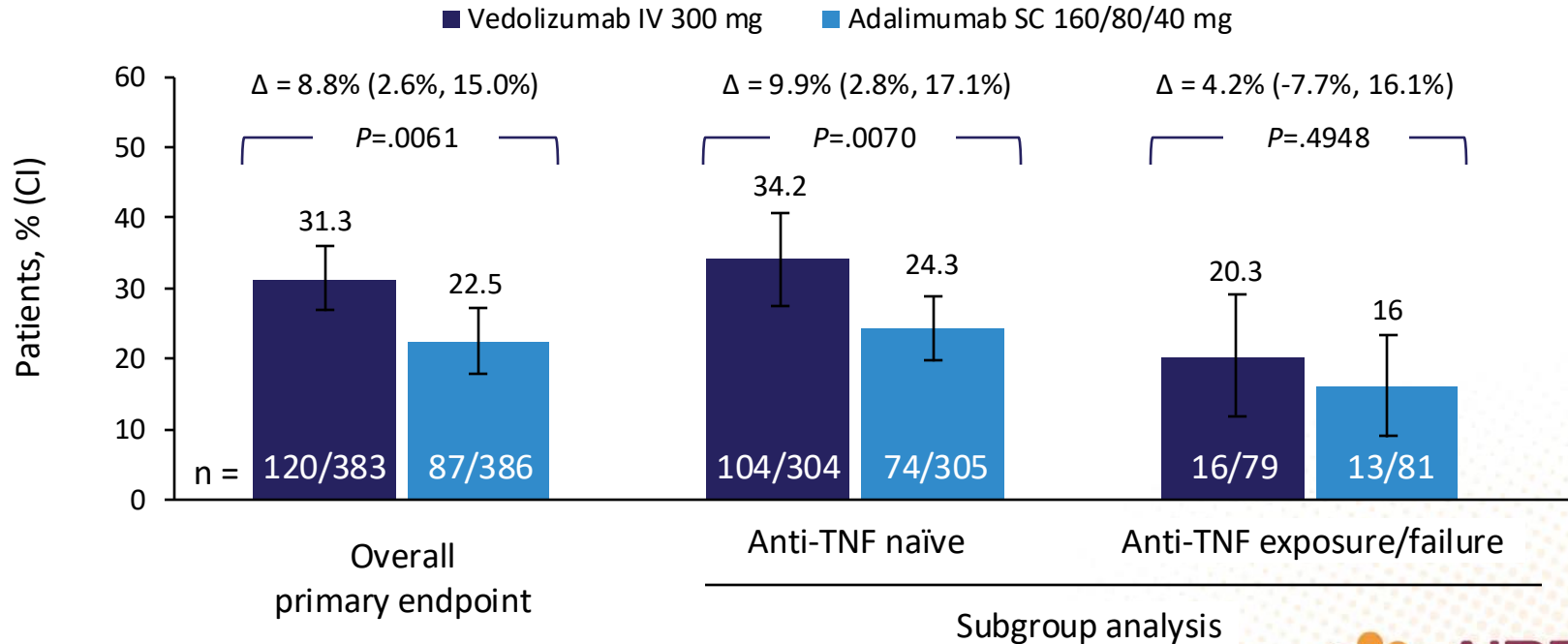
Gold standard: Designed and powered to allow formal comparison between different active therapies

RCT = randomized controlled trial.

Gurevitch J, et al. *Nature*. 2018;555(7695):175-182. Corrigan-Curay J, et al. *JAMA*. 2018;320(9):867-868. Peyrin-Biroulet L, et al. *J Crohns Colitis*. 2017;11(Suppl 2):S567-S575. Favalli EG, et al. *Biomed Res Int*. 2014;2014:831603.

Moderate-to-Severe UC: Vedolizumab > Adalimumab (VARSITY)

Clinical Remission and Mucosal Healing at Week 52



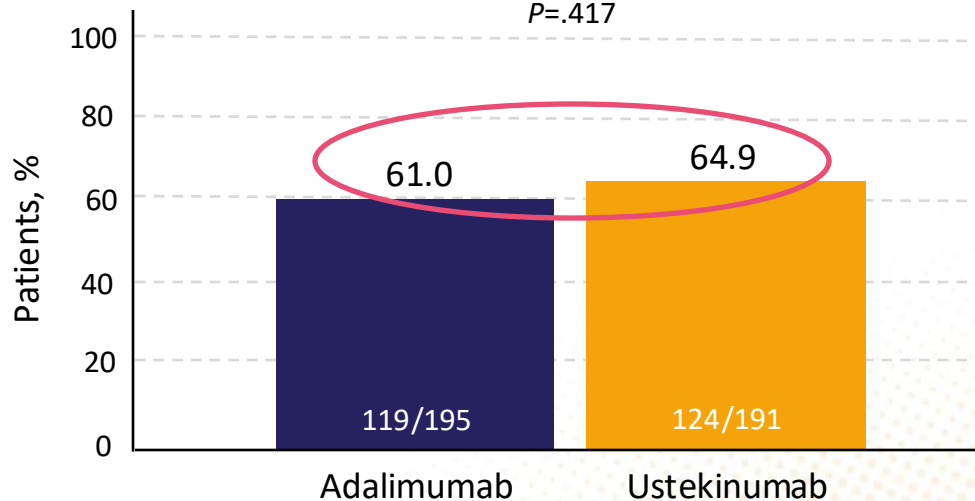
CD First-Line: Ustekinumab = Adalimumab (SEAVUE)

- Randomized, double-blinded, parallel-group, active-controlled study
- Biologic-naïve patients
- N=386; UST=191, ADA=195
- Mean disease duration
 - Ustekinumab arm: 6.8 years (SD 7.8)
 - Adalimumab arm: 6.6 years (SD 7.2)

Primary Endpoint:
Clinical Remission (CDAI <150) at Week 52

$\Delta = 4.0\%$ (95% CI: -5.5%, 13.5%)

$P=.417$



Comparative Risk of Serious Infections with Biologic Agents: A Systematic Review and Meta-Analysis

Risk of serious infections with advanced therapies for IBD

Meta-analysis of 20 head-to-head studies

Ustekinumab vs TNF α antagonists (5 cohorts; 23,232 patients)
<ul style="list-style-type: none">• CD: 51% lower risk of serious infections with ustekinumab• UC: Knowledge gap

Vedolizumab vs TNF α antagonists (17 cohorts; 51,596 patients)
<ul style="list-style-type: none">• CD: No difference in risk of serious infections (OR, 1.03)• UC: 32% lower risk of serious infections with vedolizumab

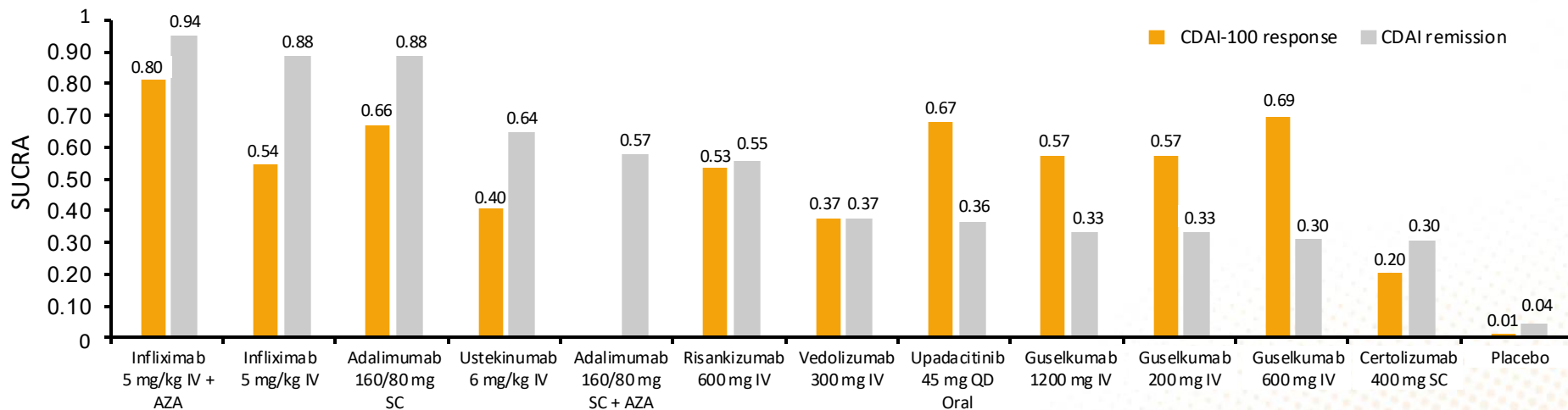
Ustekinumab vs vedolizumab (5 cohorts; 1420 patients)
<ul style="list-style-type: none">• CD: 60% lower risk of serious infections with ustekinumab• UC: Knowledge gap

Safety profile of advanced therapies for IBD varies and is influenced by treatment effectiveness and intrinsic immune suppression

Comparative Onset of Early Effect of Biologics and Small Molecules in Moderately to Severely Active Luminal CD



SUCRA ranking for induction of clinical benefit within the initial 6 weeks of treatment (overall patient population)



AZA = azathioprine; SUCRA = surface under the cumulative ranking curve.
Attaoui M, et al. *Aliment Pharmacol Ther.* 2024;60(2):124-143.

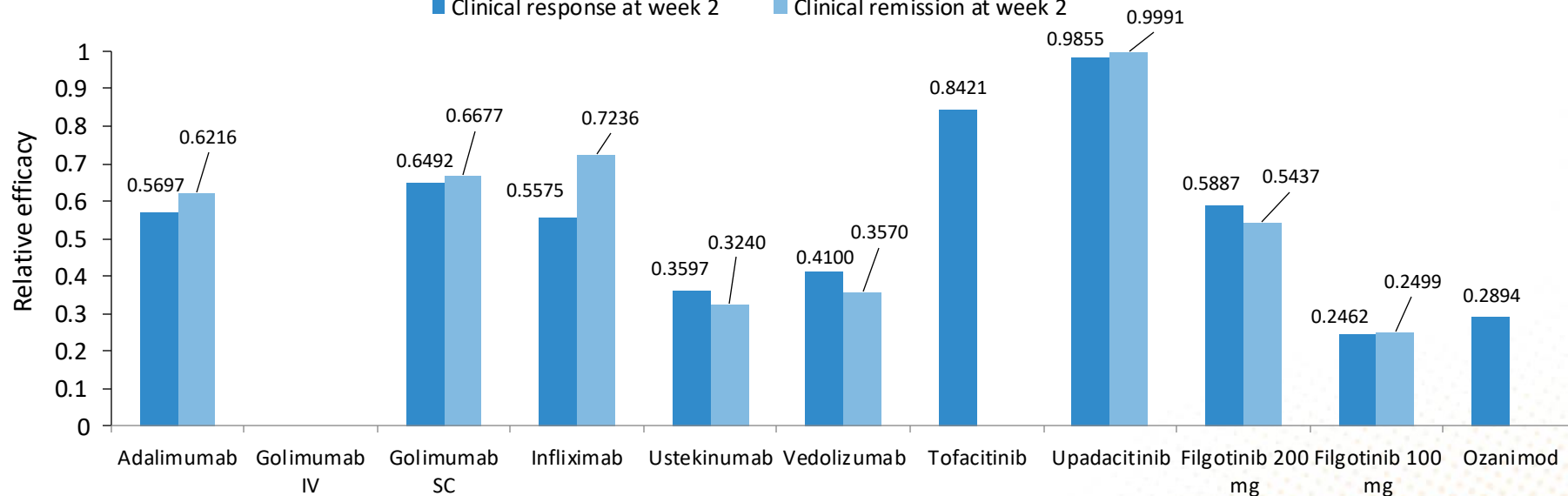
Comparative Onset of Effect of Biologics and Small Molecules in Moderately to Severely Active UC



SUCRA Ranking for Induction of Clinical Efficacy at Week 2

■ Clinical response at week 2

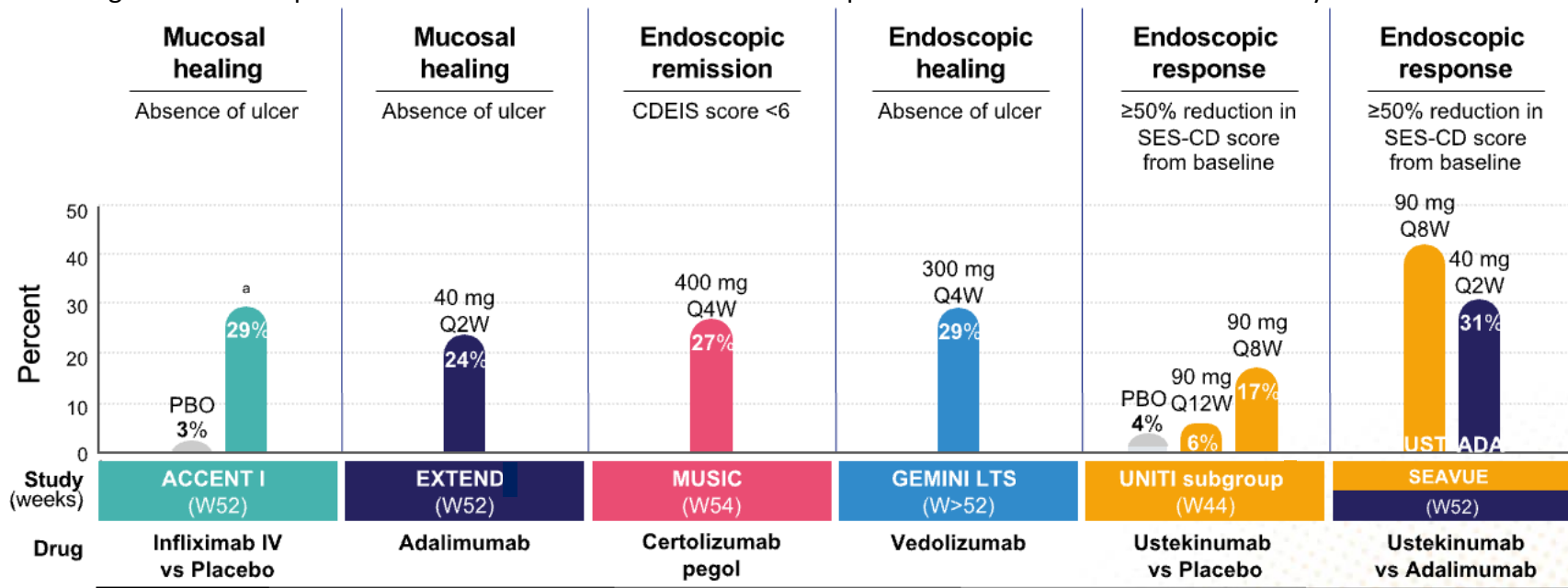
■ Clinical remission at week 2



Endoscopic Outcomes by CD Therapeutics: 1-Year Maintenance Data from Clinical Trials



- Endoscopic outcomes were collected during registrational clinical trials but used different endpoints
- Registration trials prior to 2020s either did not evaluate endoscopic outcomes or evaluated as secondary outcomes

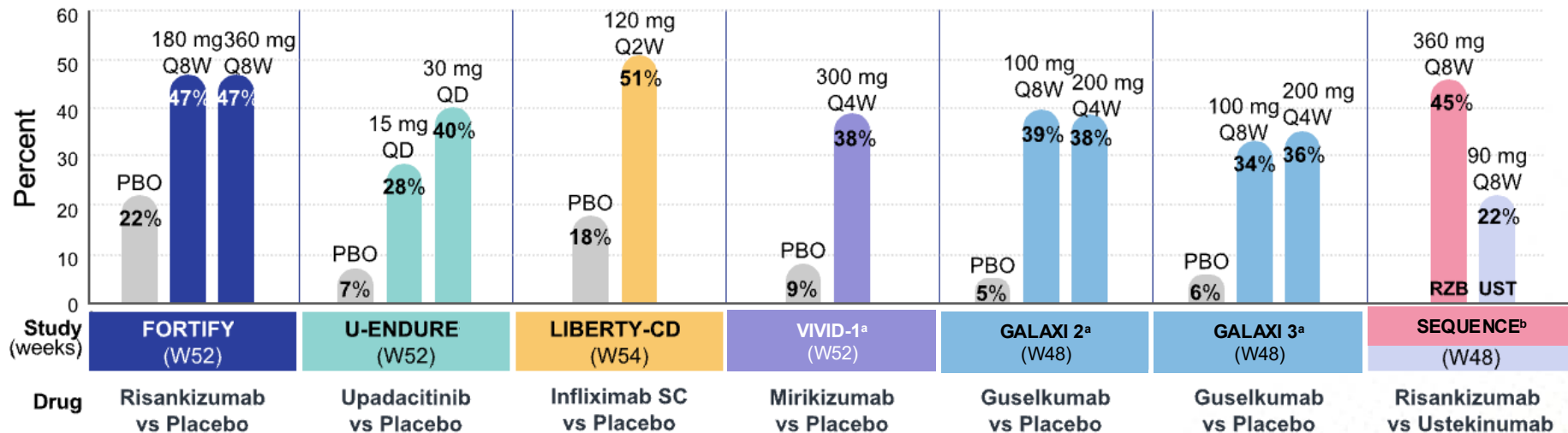


^aNot specified.

CDEIS = CD endoscopic index of severity; SES-CD = Simple Endoscopic Score for CD; LTS = long-term study; PBO = placebo. Hanauer SB, et al. *Lancet*. 2002;359(9317):1541-1549. Rutgeerts P, et al. *Gastroenterology*. 2012;142(5):1102-1111.e2. Hébuterne X, et al. *Gut*. 2013;62(2):201-208. Noman M, et al. *J Crohns Colitis*. 2017;11(9):1085-1089. Rutgeerts P, et al. *Gastroenterology*. 2018;155(4):1045-1058. Sands BE, et al. *Lancet*. 2022;399(10342):2200-2211. Neurath MF, Vieth M. *Gut*. 2023;72(11):2164-2183.

Not intended for head-to-head drug comparison.

Endoscopic Outcomes by CD Therapeutics: 1-Year Maintenance Data from Clinical Trials



Not intended for head-to-head drug comparison.

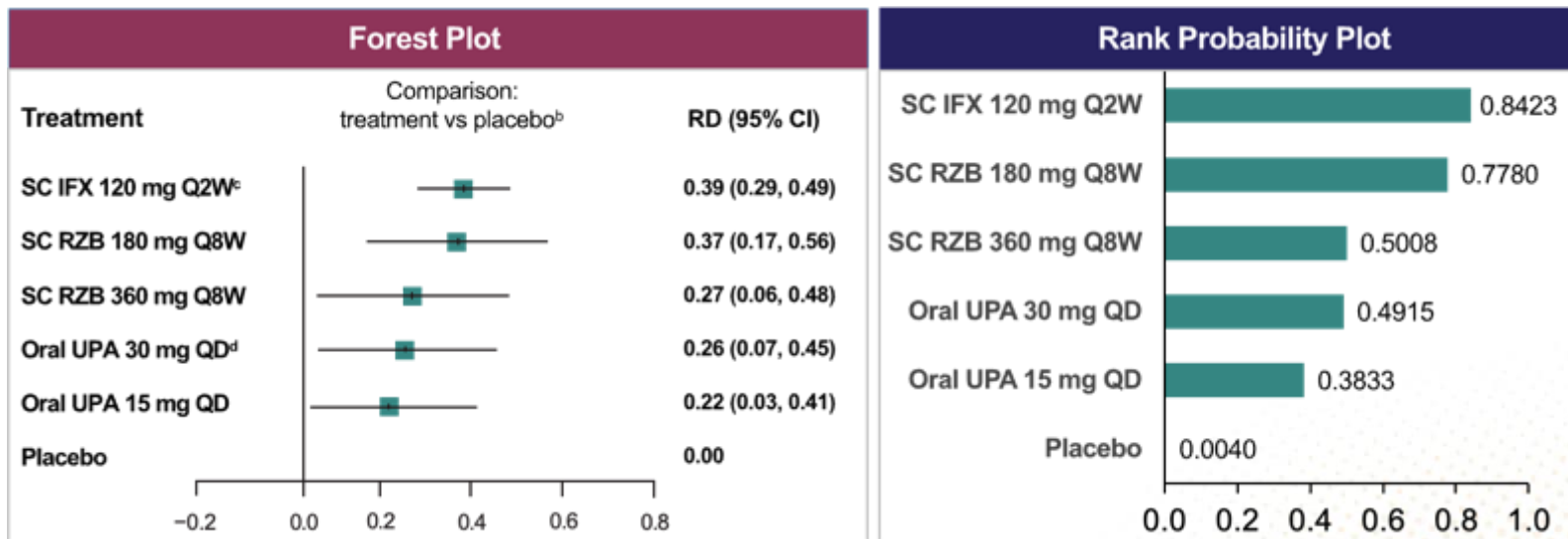
^aMirikizumab and guselkumab have been approved by the FDA for the treatment of CD; ^bEndoscopic response was the secondary endpoint for the SEQUENCE study.

FDA = US Food and Drug Administration; RZB = risankizumab.

Ferrante M, et al. *Lancet*. 2022;399(10340):2031-2046. Loftus EV Jr, et al. *N Engl J Med*. 232;388(21):1966-1980. Hanauer SB, et al. *Gastroenterology*. 2024;167(5):919-933. Ferrante M, et al. *J Crohns Colitis*. 2024;18(Suppl 1):i7-i9. Panaccione R, et al. *Gastroenterology*. 2024;166(5):1057b1. Peyrin-Biroulet L, et al. *N Engl J Med*. 2024;391(3):213-223. Neurath MF, Vieth M. *Gut*. 2023;72(11):2164-2183.

Comparison of Endoscopic Response Rate in First-Line-Use Patients

SC IFX 120 mg Q2W showed the highest risk difference for achieving endoscopic response^a (0.39 [0.29-0.49]) during the maintenance phase. In terms of rank probability plot, SC IFX 120 mg Q2W demonstrated the highest *P*-score.



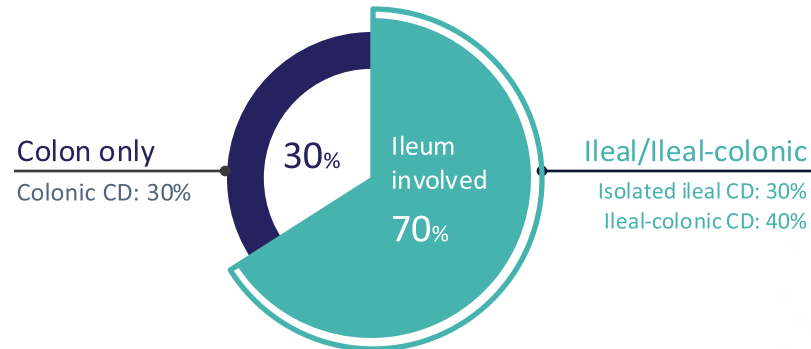
Data were synthesized in a frequentist NMA random-effects model that included all evaluated dosing regimens (including dose escalation).

^aEndoscopic response: $\geq 50\%$ decrease in SES-CD from baseline. ^bRandom-effects model. ^c36 out of 205 patients received dose escalation (240 mg Q2W) upon secondary loss of response. ^dEscalated dose on the US FDA label. RD = risk difference; UPA = upadacitinib.

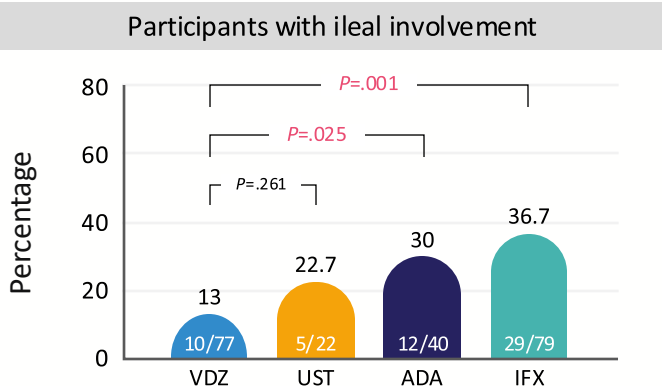
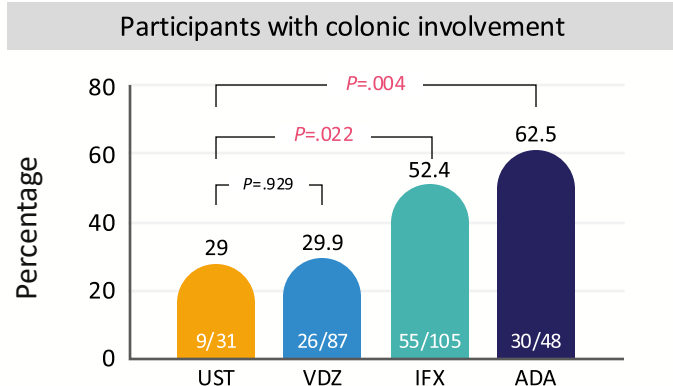
Schreiber S, et al. *J Crohns Colitis*. 2024;18(Suppl 1):i1189-i1190. Presented at: ECCO Congress; 2024. P623.

Why Should We Care about Segmental Healing?

- About 70% of patients with CD have ileal involvement (30% with isolated ileal disease), and the terminal ileum is often the most difficult to treat
- While TNF- α inhibitors have been demonstrated to be one of the most effective drugs in achieving endoscopic healing in ileal CD, it is still more challenging than for colonic segments



Pooled analysis of four biologics on 1-year endoscopic healing rate by involved segments



VDZ = vedolizumab.

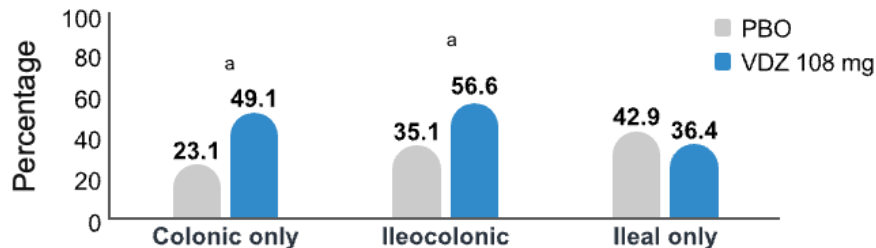
Richard N, et al. *World J Gastroenterol.* 2023;29(21):3222-3240. Dulai PS, et al. *Clin Gastroenterol Hepatol.* 2019;17(13):2634-2643. Narula N, et al. *Am J Gastroenterol.* 2022;117(7):1106-1117.

IBD Therapeutics Show Lower Efficacy in Isolated Ileal Disease

Advanced therapies vary in their ability to treat CD affecting different locations

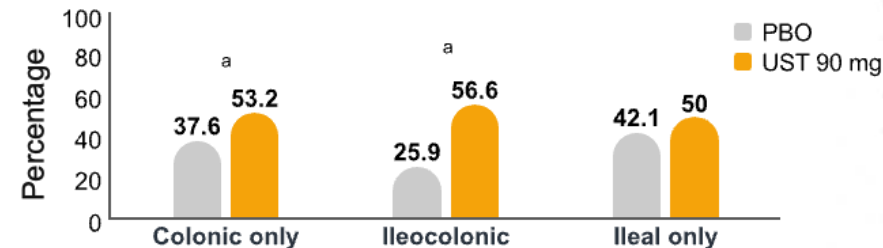
VDZ SC (VISIBLE 2)

Clinical Remission at Week 52



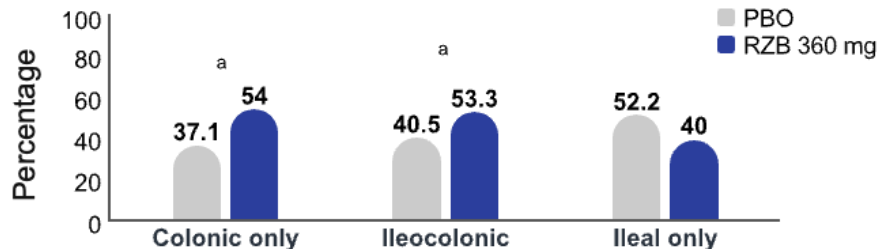
UST SC (IM-UNITI)

Clinical Remission at Week 44



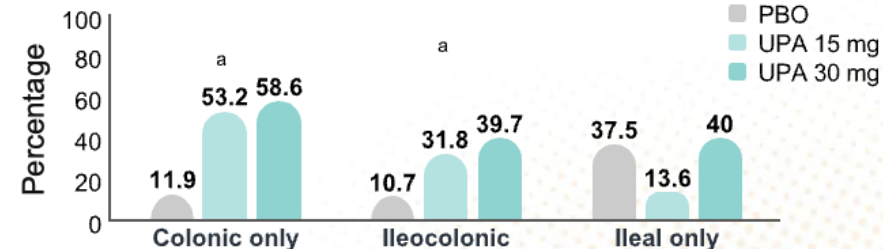
RZB SC (FORTIFY)

Clinical Remission at Week 52



UPA (U-ENDURE)

Clinical Remission at Week 54

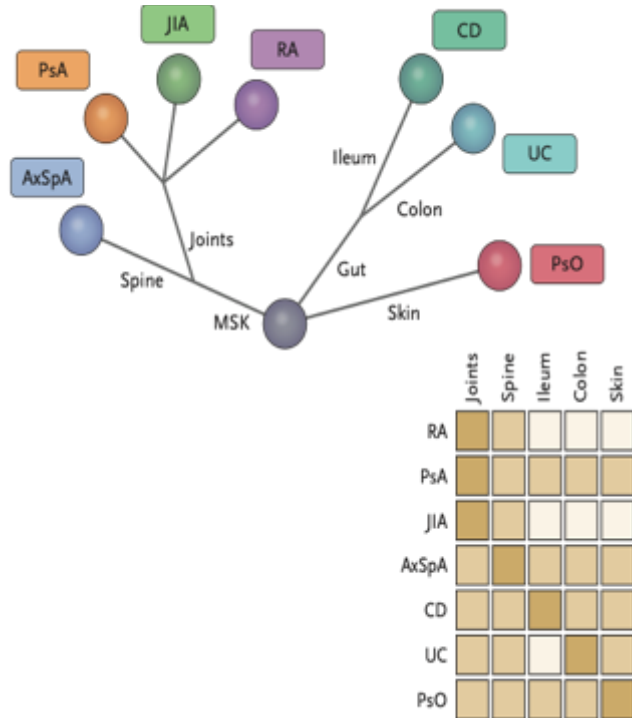


^aStatistically significant.

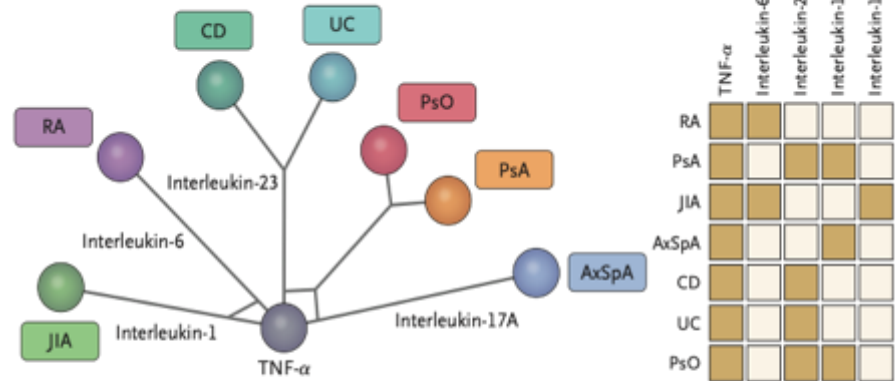
Vermeire S, et al. *J Crohns Colitis*. 2022;16(1):27-38. Feagan BG, et al. *N Engl J Med*. 2016;375(20):1946-1960. Ferrante M, et al. *Lancet*. 2022;399(10340):2031-2046. Loftus EV Jr, et al. *N Engl J Med*. 2023;388(21):1966-1980. Atreya R, et al. *Curr Res Pharmacol Drug Discov*. 2022;3:100097.

TNF Is an “Upstream” Cytokine

Organ-Based Concept



Signature Cytokine-Based Concept

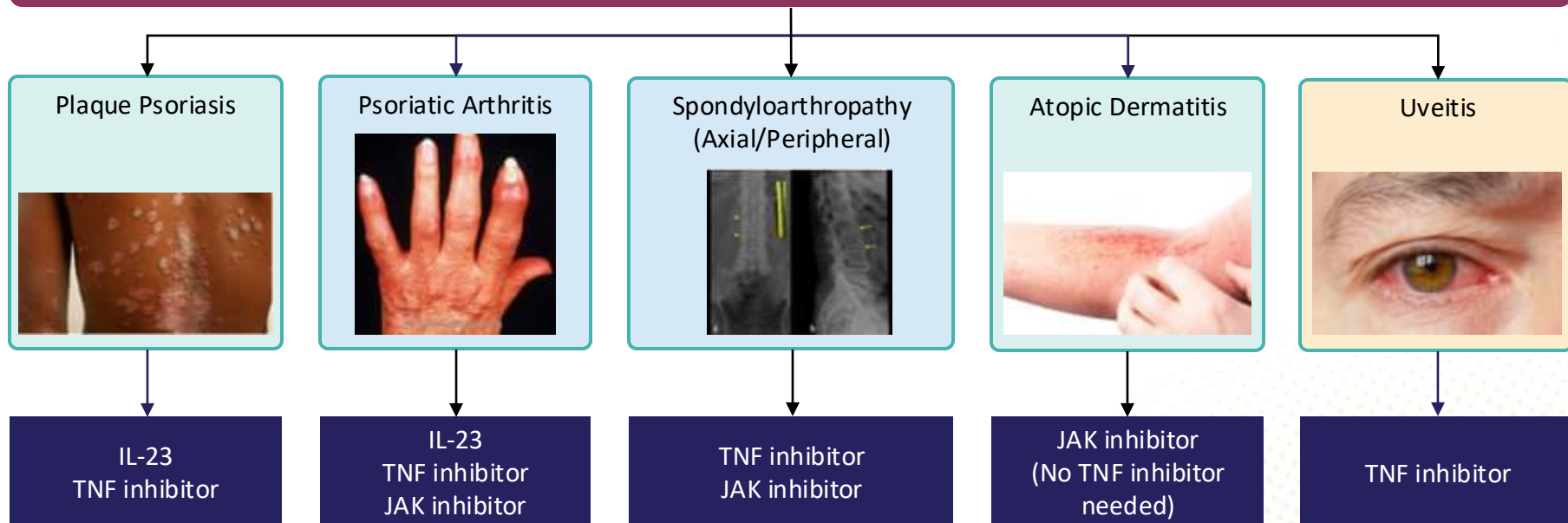


AxSpA = axial spondyloarthritis; JIA = juvenile idiopathic arthritis; PsA = psoriatic arthritis; PsO = psoriasis;
RA = rheumatoid arthritis.

Schett G, et al. *N Engl J Med*. 2021;385(7):628-639.

Choosing Advanced Therapies for UC Based on Concomitant Immune Conditions and Extraintestinal Manifestations

Coexisting EIMs with IBD



EIM = extraintestinal manifestation; IL = interleukin.
Courtesy of Rubin DT.

Summary: TNF α Inhibitors for the Treatment of IBD: Therapeutic Advances and Innovative Delivery Methods



- Use what you know: We know THE MOST about anti-TNFs
- They are EFFECTIVE, especially when used EARLY and FIRST
- They are great for extraintestinal manifestations
- They demonstrate improvement in clinical response and promote mucosal healing
- They are safer than inadequate disease control
- Anti-TNF (infliximab) is still primary choice in hospitalized ASUC and for perianal disease
- They are a “gateway to JAK inhibitors” when you need something next
- They are AVAILABLE TO US
- They are (now) AFFORDABLE (relatively speaking!)
 - Early effective therapy reduces downstream costs (hospitalizations, surgery)
 - Biosimilars increase access
 - Subcutaneous formulations may reduce systems-level costs

Real-Life Challenges in IBD: Exploring Anti-TNF Treatment Strategies in Context of a Complex Case Scenario

Meet Patient A



Presentation/Background

- Female
- Age 28
- Crohn's disease x 18 months
- Terminal ileum involvement

Parameter	Details
Initial SES-CD	9 (moderate disease)
Imaging	Intestinal ultrasound: terminal ileitis
Treatment to date	Budesonide, vedolizumab infusions (non-adherent)
Current symptoms	GI: pain, diarrhea, weight loss, fatigue, blood on paper
EIMs	Joint pain (knees, ankles)
Exam	RLQ tenderness, large edematous perianal skin tag

Clinical Red Flags



GI symptoms despite steroids → active inflammation



Ongoing extraintestinal manifestations → systemic involvement



Perianal findings → high-risk phenotype



Non-adherence to vedolizumab → suboptimal maintenance



No evidence of stricture / fistula → still early enough for disease modification

Why Anti-TNF, and Why Now?

Indication	Evidence
Small bowel CD	Early anti-TNF linked to better outcomes (SONIC, PROFILE)
EIMs (arthritis)	Anti-TNF effective across joint, skin, ocular domains
Perianal disease	Infliximab is ideal therapy for complex perianal CD
Disease progression	Delay = fibrosis, strictures, loss of window of opportunity

Key Learning Points

This patient is ready for biologics—anti-TNF offers the right match for phenotype and urgency

Extraintestinal and perianal signs should accelerate treatment plans

Use TDM, education, and early intervention to optimize outcomes

Don't wait for complications to escalate—act early