Updates in Crohn's Disease Management

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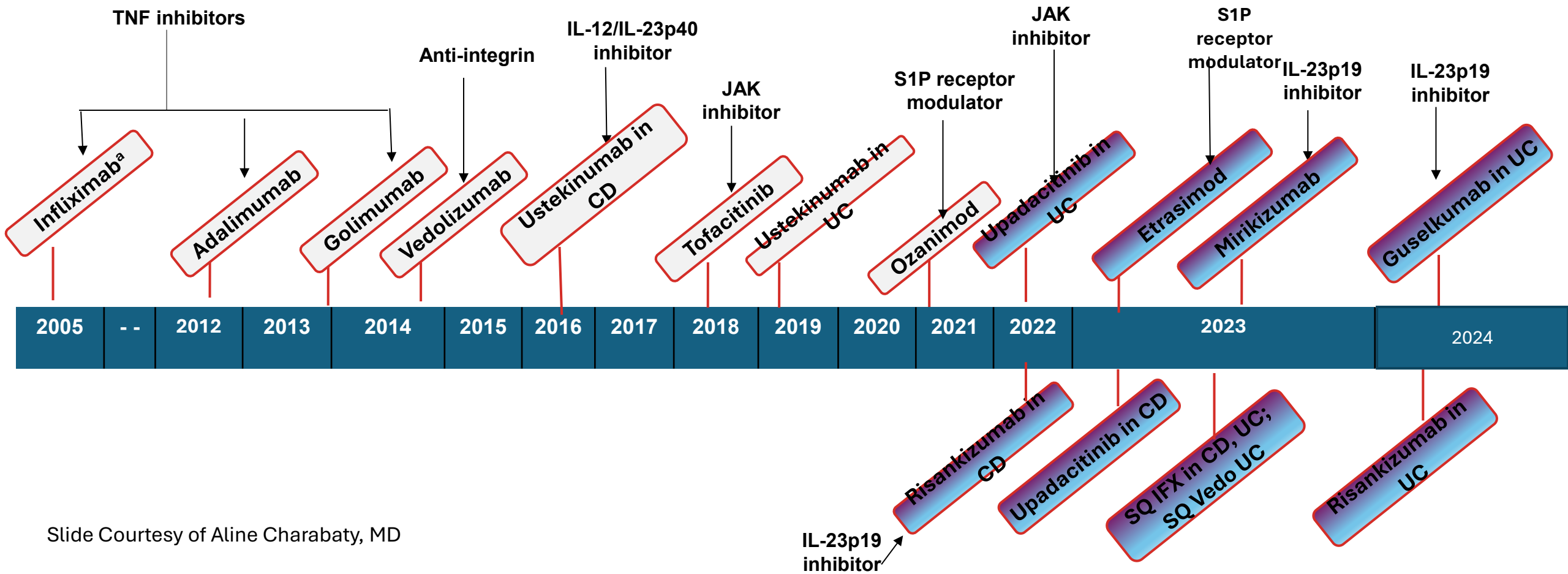
Objectives

- Review updated guidelines in management of Crohn’s Disease
- Review new medications approved for Crohn’s Disease
- Management of Crohn’s Disease in special populations

Timeline of FDA Approvals of Therapies for Mod-Severely Active UC or CD



Slide Courtesy of Aline Charabaty, MD

Case 1:

- 40 y/o F with history of moderate ileocolonic Crohn's disease. She was diagnosed in her 20s and has been on Infliximab for 10 years for both her Crohn's disease and peripheral arthritis. She was most recently on Infliximab but has developed antibodies. Her most recent colonoscopy showed ulcerations in both the right colon and terminal ileum. What would you suggest next?
    - 1) Try another anti-TNF such as Humira
    - 2) Switch to Vedolizumab
    - 3) Switch to Upadacitinib
    - 4) Switch to Ozanimod

Assessing Disease Severity

Low Risk

- Age at diagnosis >30 y/o
- Limited anatomic involvement, colonic versus ileal, ileocolonic or upper GI
- No perianal or severe rectal disease
- Superficial ulcers
- No prior surgical resection
- No structuring/penetrating behavior

Moderate/High Risk

- Age at diagnosis < 30 y/o
- Extensive anatomic involvement
- Perianal/severe rectal disease
- Deep ulcers
- Prior surgical resection
- Stricturing/penetrating disease

Sandborn WJ. Gastroenterology. 2014;147(3):702-703.
Lichtenstein GR et al. Am J Gastroenterolo. 2025;120(6):1225-1264

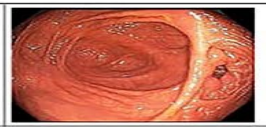
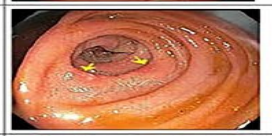
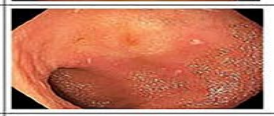
Endoscopic score

CROHN'S DISEASE

Simple Endoscopic Score for CD (SES-CD) – grade given to each of 5 segments (ileum, right colon, transverse colon, left colon, and rectum)

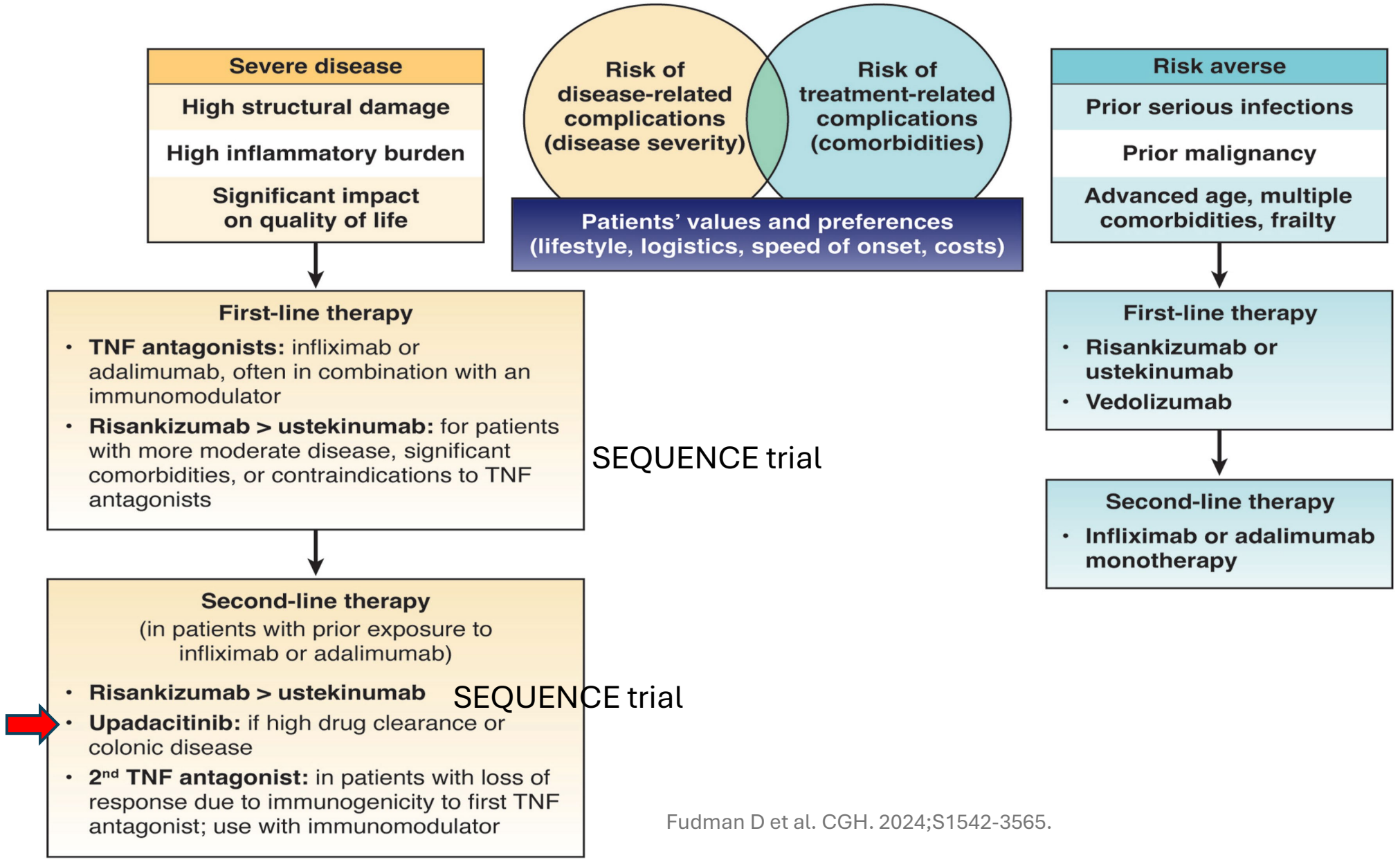
Ulcerated surface	0: none	1: <10%	2: 10%-30%	3: >30%
Size of ulcers	0: None	1: <0.5 cm	2: Large ulcers 0.5-2 cm	3: very large ulcers >2 cm
Affected surface	0: None	1: <50%	2: 50%-75%	3: >75%
Presence of narrowing	0: None	1: Single and transversable	2: Multiple and transversable	3: Non-transversable

Postoperative Crohn's Disease - Rutgeert's Score

i0	Normal neo-terminal ileum	
i1	≤5 aphthous erosions in the neo-terminal ileum	
i2	>5 aphthous erosions in the neo-terminal ileum	
i2a	Ulcers confined to the ileocolonic anastomosis	
i2b	Ulcers that involve the ileocolonic anastomosis and extend proximally to involve the neoterminal ileum	

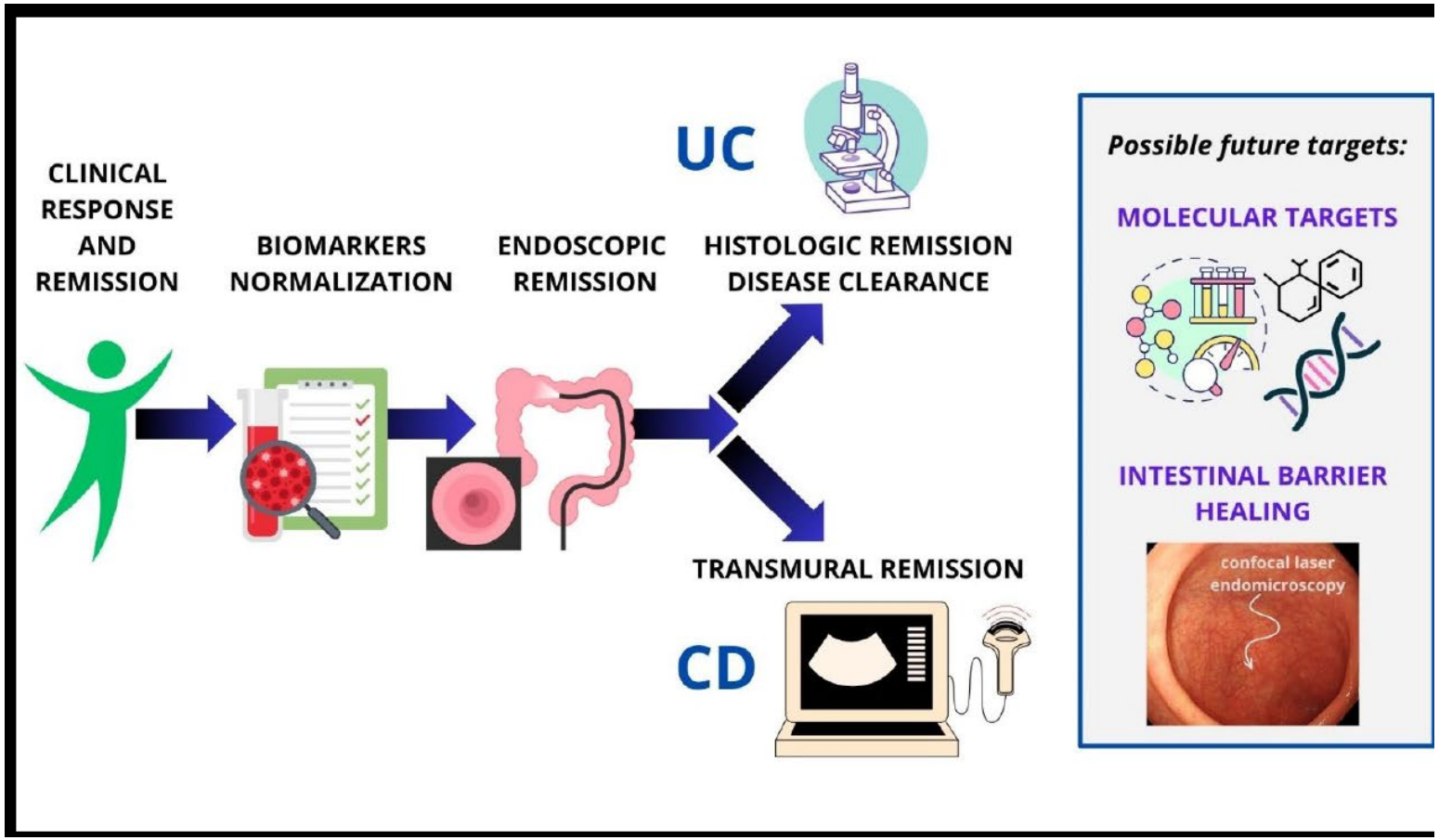
Gaidos, Jill K.J.; Hashash, Jana G.Official journal of the American College of Gastroenterology | ACG120(8):1732-1741, August 2025.

Treatment Algorithm for Moderate to Severe Crohn's Disease



Fudman D et al. CGH. 2024;S1542-3565.

Evolution of Targets in Treatment



Centanni L et al. Pharmaceuticals. 2025.

Disease Activity Monitoring

Table 2. Disease activity monitoring

Treatment target	Clinical response	Clinical and biochemical remission	Endoscopic remission	Proactive monitoring
Timing of assessment	6–12 wk	3–6 mo	6–12 mo	Every 6–12 mo
Definitions based on modality of assessment	• Improvement in clinical symptoms (decrease in disease activity score) • Decrease in CRP and/or FC • Improvement in intestinal ultrasound (i.e. decrease in bowel wall thickness and/or decreased hypervascularity)	• Absence of clinical symptoms • Normalization of CRP and/or FC (<150 ± 50 μg/g (5) or 100–250 μg/g (2)) • Normalization of intestinal ultrasound (i.e. bowel wall thickness <3 mm, no hypervascularity, intact bowel wall stratification)	• CD: SES-CD < 3 or absence of ulcerations (2) • UC: Mayo Endoscopic Score = 0 or UCEIS ≤ 1 (2) or FC < 150 ± 50 μg/g (5)	• Disease activity assessment • CRP and/or FC

CD, Crohn's disease; CRP, C-reactive protein; FC, fecal calprotectin; SES, Simple Endoscopic Score; UC, ulcerative colitis; UCEIS, UC Endoscopic Index of Severity.

OFFICIAL JOURNAL OF THE AMERICAN COLLEGE OF GASTROENTEROLOGY | ACG

Gaidos, Jill K.J.; Hashash, Jana G.Official journal of the American College of Gastroenterology | ACG120(8):1732-1741, August 2025.

Medication category	TNF (inhibitor) IFX, ADA, CTZ (CD), GOL (UC)	Anti-Integrin (VDZ)	Anti-IL23 +/-12 (UST, RISA, MIR, GUS)	JAK I (tofa/upa)
Indications	UC/CD	UC/CD	UC/CD	UC for tofa, CD/UC Upa
Formulations; placement	IV and SQ, rapid onset of action	IV and SQ Better if used in TNF naive	IV induction→SQ maintenance Fast onset of action Effective in both TNF naïve and failure Mir decrease bowel urgency	Oral Rapid onset of action Effective in both TNF naïve and filature
EIMs/autoimmune conditions	**EIMS, perianal with IMM**	**Gut selective**	**Psoriasis, PSA**	**RA, psoriasis, atopic derm, AS, spondylarthritis, peripheral arthritis**
Risks/Side effects	Immunogenic, lymphoma with IMM, infection risk	Low immunogenicity, good safety profile	Low immunogenicity	Herpes, MACE, VTE (RA studies > UC studies)
Pregnancy/lactation safe	yes	yes	UST safe	no

The NEW ENGLAND JOURNAL of MEDICINE

RESEARCH SUMMARY

Upadacitinib Induction and Maintenance Therapy for Crohn's Disease

Loftus EV Jr. et al. DOI: 10.1056/NEJMoa2212728

CLINICAL PROBLEM

Treatment options with new mechanisms of action are needed for patients with moderate-to-severe Crohn's disease. Upadacitinib — an oral, reversible Janus kinase (JAK) inhibitor — showed promise for treatment of Crohn's disease in a phase 2 trial.

CLINICAL TRIALS

Design: Two multinational, phase 3, double-blind, randomized, placebo-controlled induction trials (U-EXCEL and U-EXCEED) and one maintenance trial (U-ENDURE) evaluated the efficacy and safety of upadacitinib in adults with moderate-to-severe Crohn's disease.

Intervention: 1021 patients were assigned to receive induction therapy with upadacitinib (45 mg) or placebo (2:1 ratio) once daily for 12 weeks; 502 who had a clinical response at week 12 were then assigned to receive maintenance therapy with upadacitinib (15 mg or 30 mg) or placebo (1:1:1 ratio) once daily for 52 weeks. The primary end points — clinical remission and endoscopic response — were evaluated at week 12 of induction treatment and week 52 of maintenance treatment.

RESULTS

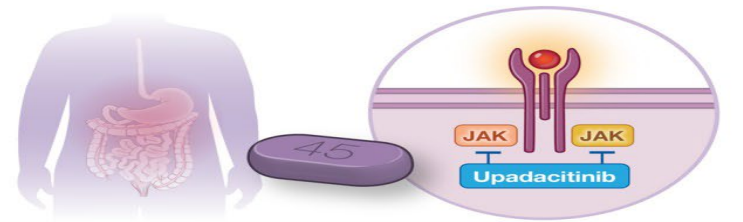
Efficacy: Upadacitinib was superior to placebo with respect to clinical remission and endoscopic response in both induction trials and in the maintenance trial.

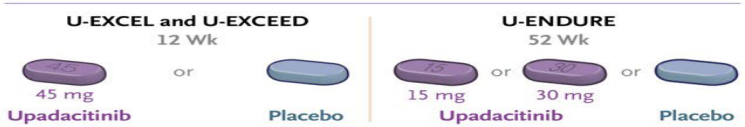
Safety: The frequencies of any, serious, and severe adverse events were similar across the groups at week 12 of induction and week 52 of maintenance. Herpes zoster, hepatic disorders, and neutropenia were more common with some doses of upadacitinib than with placebo.

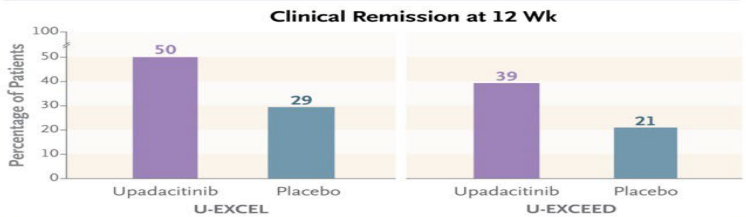
LIMITATIONS AND REMAINING QUESTIONS

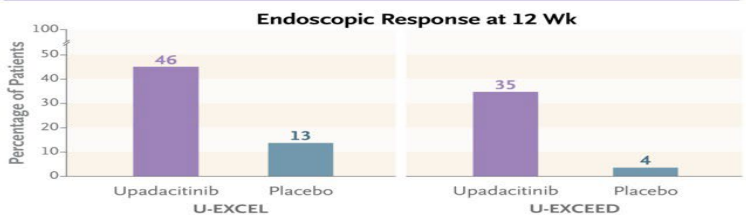
- The trials could not identify adverse events that were rare or had a long latency. The ongoing extension study of U-ENDURE will continue to evaluate safety for up to 5 years.

Links: Full Article | NEJM Quick Take | Science behind the Study









CONCLUSIONS

In patients with moderate-to-severe Crohn's disease, induction and maintenance treatment with the JAK inhibitor upadacitinib was associated with higher percentages of patients with clinical remission and endoscopic response than receipt of placebo.

Loftus EV et al. NEJM 2023;388-1966-80

Upadacitinib – approved for CD

- 45mg daily for 12 wks, then 15-30mg daily
- Recent publication of U-EXCEL/U-EXCEED and U-ENDURE looking at UPA vs placebo in mostly TNF experienced pts
  - Clinical response (CDAI score) seen by 2 wks, and remission by 4 weeks
  - Clinical remission week 52 - 47.6% (UPA 30mg), 37.3% (15 mg) vs 15.1% (placebo)
  - Endoscopic response week 52 – 40.1% (30 mg), 27.6% (15 mg) vs 7.3%
  - Increased risk for herpes zoster (dose effect); no increased risk for VTE, MACE

Loftus EV et al. NEJM 2023;388-1966-80

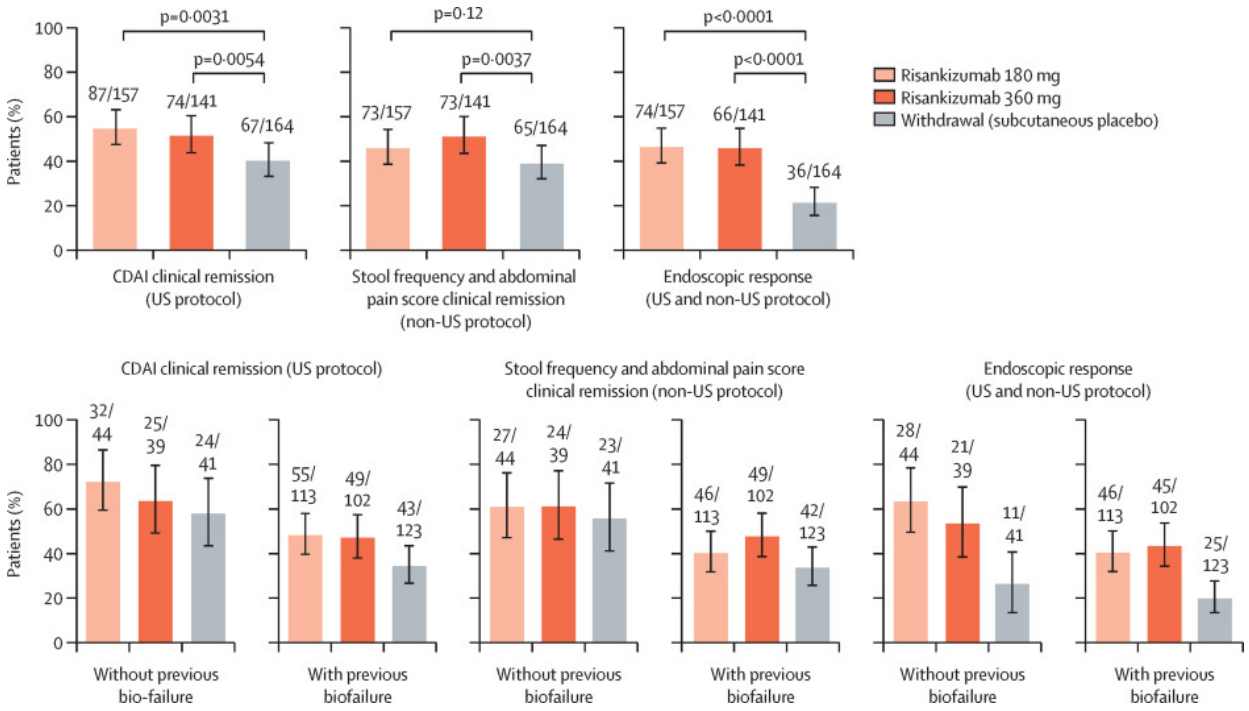
Risankizumab – CD- approved 2022

- ADVANCE and MOTIVATE showed IV Risa effective and well tolerated induction therapy
- FORTIFY phase 3, randomized, double-blind, placebo-controlled, maintenance withdrawal study
- Moderate to severe CD and in FORTIFY: randomized 1:1:1 to 180 mg SC Risa, 360 mg SC or withdrawal (q8 wks)
  - 712 pts assessed, 542(from ADVANCE AND MOTIVATE) randomly assigned to risa 180 (157) or Risa 360 (141), placebo (164)
- 73% pts categorized as previous bio-failure

Ferrante M et al. Lancet 2022;399:2031-46

Risankizumab – 52 wk data

- Greater clinical and endoscopic response rates reached with 360 mg vs placebo, 52% vs 41%, 47% vs 22% (endoscopic) similar to 180 mg dose
- Risa safe and effective for pts with moderate to severe CD
- No new safety risks
- Dosing: 600 mg IV, wks 0, 4, 8 followed by 360 mg or 180 mg every 8 wks
- Can see clinical improvement within 2 wks of initial IV Dose



Ferrante M et al. Lancet 2022;399:2031-46

The NEW ENGLAND JOURNAL of MEDICINE

Risankizumab vs. Ustekinumab for Crohn's Disease

A PLAIN LANGUAGE SUMMARY

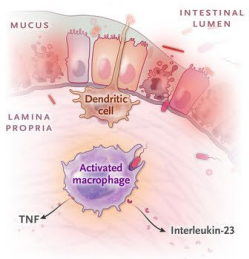
Based on the NEJM publication: Risankizumab versus Ustekinumab for Moderate-to-Severe Crohn's Disease by L. Peyrin-Biroulet et al. (published July 18, 2024)

In this trial, researchers compared the efficacy and safety of risankizumab and ustekinumab in patients with moderate-to-severe Crohn's disease.

In patients with moderate-to-severe Crohn's disease, tumor necrosis factor (TNF) inhibitors are the preferred first-line advanced therapy.

WHY WAS THE TRIAL DONE?

Some patients with moderate-to-severe Crohn's disease have an inadequate response to first-line advanced therapy with TNF inhibitors or unacceptable side effects. Robust data from head-to-head clinical trials are needed to assist clinicians in selecting an alternative biologic agent for these patients.



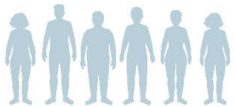
HOW WAS THE TRIAL CONDUCTED?

527 adults with moderate-to-severe Crohn's disease were assigned to receive risankizumab or ustekinumab at standard doses for 48 weeks. Two primary end points were tested sequentially: clinical remission at week 24 (a noninferiority analysis in the first 50% of enrolled patients, with a noninferiority margin of 10 percentage points) and endoscopic remission at week 48 (a superiority analysis in 100% of patients).

255 Patients

265 Patients

PATIENTS



WHO

527 adults

Mean age, 38 years

CLINICAL STATUS

Confirmed diagnosis of moderate-to-severe Crohn's disease at least 3 months before enrollment

Inadequate response to at least one TNF inhibitor or unacceptable side effects

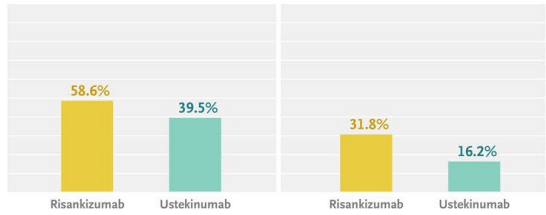
No previous exposure to any advanced therapy except TNF inhibitors

TRIAL DESIGN

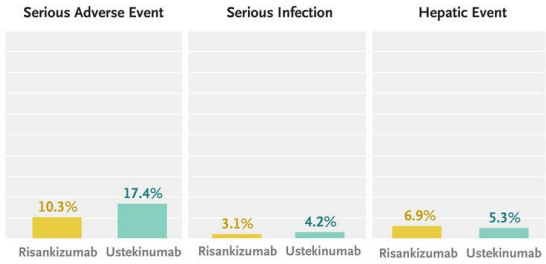
- PHASE 3B
- RANDOMIZED
- CONTROLLED
- OPEN-LABEL
- BLINDED ASSESSMENT OF END POINTS
- LOCATION: 187 SITES IN 28 COUNTRIES

RESULTS

Risankizumab was noninferior to ustekinumab for clinical remission at week 24 and superior for endoscopic remission at week 48.



Serious adverse events occurred less frequently with risankizumab than with ustekinumab. The incidence of serious infection and hepatic events was similar in the two groups.



LIMITATIONS AND REMAINING QUESTIONS

- The open-label trial design might have influenced reporting of symptoms and safety events.

CONCLUSIONS

In patients with moderate-to-severe Crohn's disease who had an inadequate response or unacceptable side effects with anti-TNF therapy, risankizumab was noninferior to ustekinumab for clinical remission at week 24 and superior for endoscopic remission at week 48.

LINKS: FULL ARTICLE | NEJM QUICK TAKE | EDITORIAL

FURTHER INFORMATION

Trial registration: ClinicalTrials.gov number, NCT04524611

Trial funding: AbbVie

Full citation: Peyrin-Biroulet L, Chapman JC, Colombel J-F, et al. Risankizumab versus ustekinumab for moderate-to-severe Crohn's disease. N Engl J Med 2024;391:213-23. DOI: 10.1056/NEJMoa2314585

Peyrin-Biroulet, L. et al. NEJM. 2024;391:213-223.

SEQUENCE Study- head-to-head

- Ustekinumab vs Risankizumab in moderate to severe CD (CDAI 220-450)
- TNF experienced
- Open label trial, centrally read endoscopy (blinded)
- Primary endpoints
  - Clinical remission at 24 weeks (CDAI < 150)
  - Endoscopic remission at 48 weeks (Simple Endoscopic Score: score <4, decrease of >2 points from baseline and no subscore >1)
- 520 pts enrolled (255 Risa and 265 Ust)

Peyrin-Biroulet, L. et al. NEJM. 2024;391:213-223.

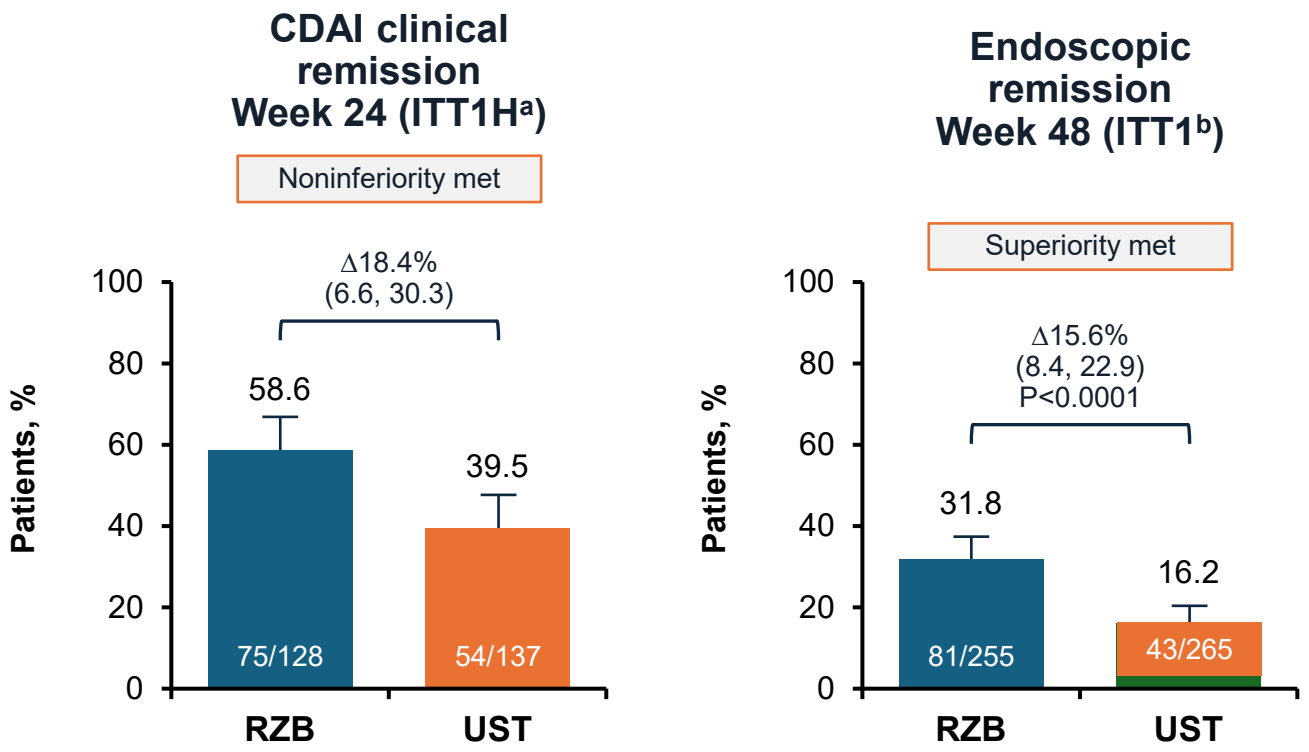
SEQUENCE: RISA vs UST in Mod-Severe TNFi-Exposed CD: Non-Inferiority Study

Demographic summary

- Mean age: ~38 years
- Mean disease duration: ~9 years
- Mean SES-CD: ~14
- Mean FCal >1000 mg/kg
- ~1/4 of patients had failed >1 anti-TNF
- Disease location:
  - Ileal (17%)
  - Colonic (40%)
  - Ileocolonic (43%)

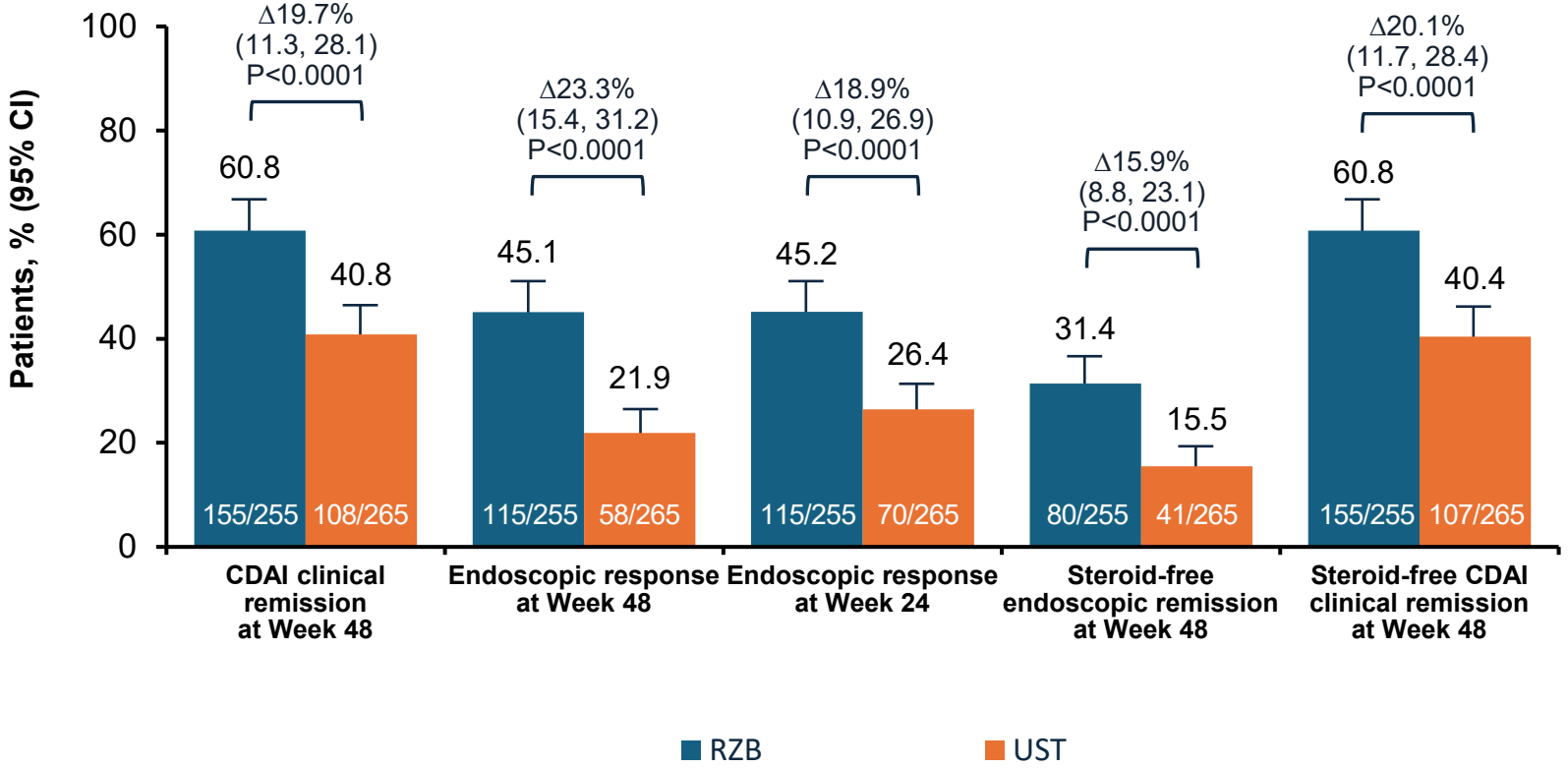
Analysis stratified for biologic exposure and corticosteroid exposure

Primary endpoints: Clinical remission, endoscopic remission



Nominal P<0.01 from a post-hoc analysis testing for superiority.
[a]ITT1H population: subset of ITT1 population that included the first ~50% of ITT1 patients.
[b]ITT1 population that included patients randomized to UST or RZB (600 mg IV, 360 mg SC) who received at least one dose of study drug.
anti-TNF, anti-tumour necrosis factor; CDAI, Crohn's disease activity index; FCal, fecal calprotectin; ITT, intention-to-treat; IV, intravenous; RZB, Risankizumab; SC, subcutaneous; SES-CD, simple endoscopic score for CD; UST, Ustekinumab.
Peyrin-Biroulet L et al. UEGW 2023. Abstract LB01.

SEQUENCE: RISA vs UST in TNFi-Exposed CD: Secondary Endpoints



Superiority met for all secondary endpoints

Efficacy:

- RZB was noninferior to UST in achieving clinical remission at Week 24
- RZB was superior to UST in achieving endoscopic remission at Week 48

Safety

- No new safety signal
- Similar incidence of TEAEs between groups
- AEs leading to study drug discontinuation were numerically lower with RZB vs UST

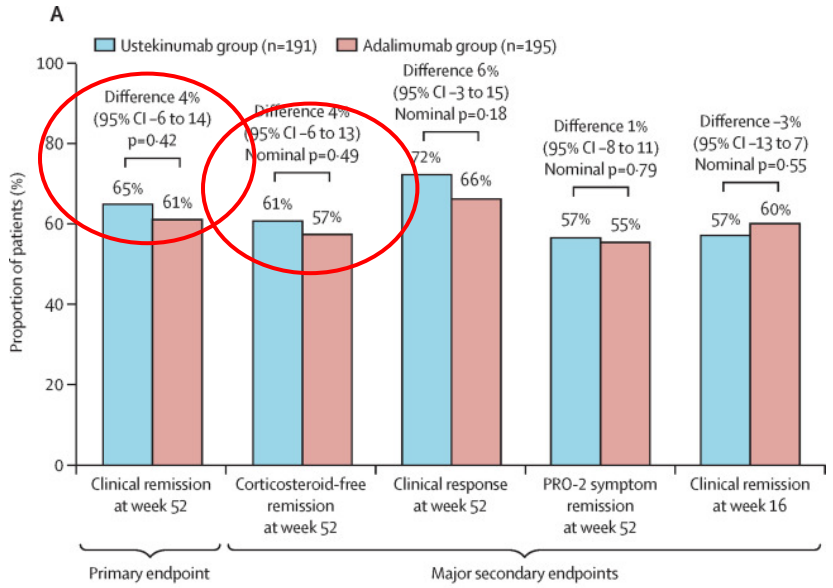
AE, adverse event; CDAI, Crohn's disease activity index; RZB, Risankizumab; TEAE, treatment-emergent adverse event; UST, ustekinumab

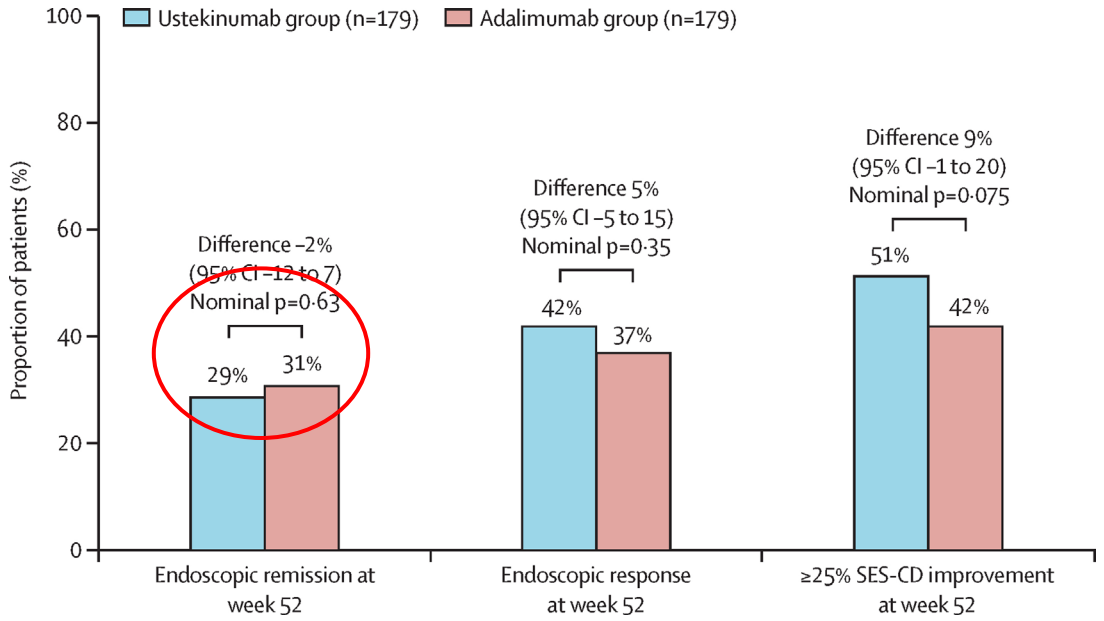
Peyrin-Biroulet L et al. UEGW 2023. Abstract LB01.

SEQUENCE Summary

- In a population of TNF failures, risankizumab superior to ustekinumab in clinical and endoscopic end points including steroid-free clinical remission and endoscopic remission
- Of note, no dose escalation allowed in ustekinumab group
  - In practice up to 40-50% of patients require more frequent dosing
- Safety signals similar

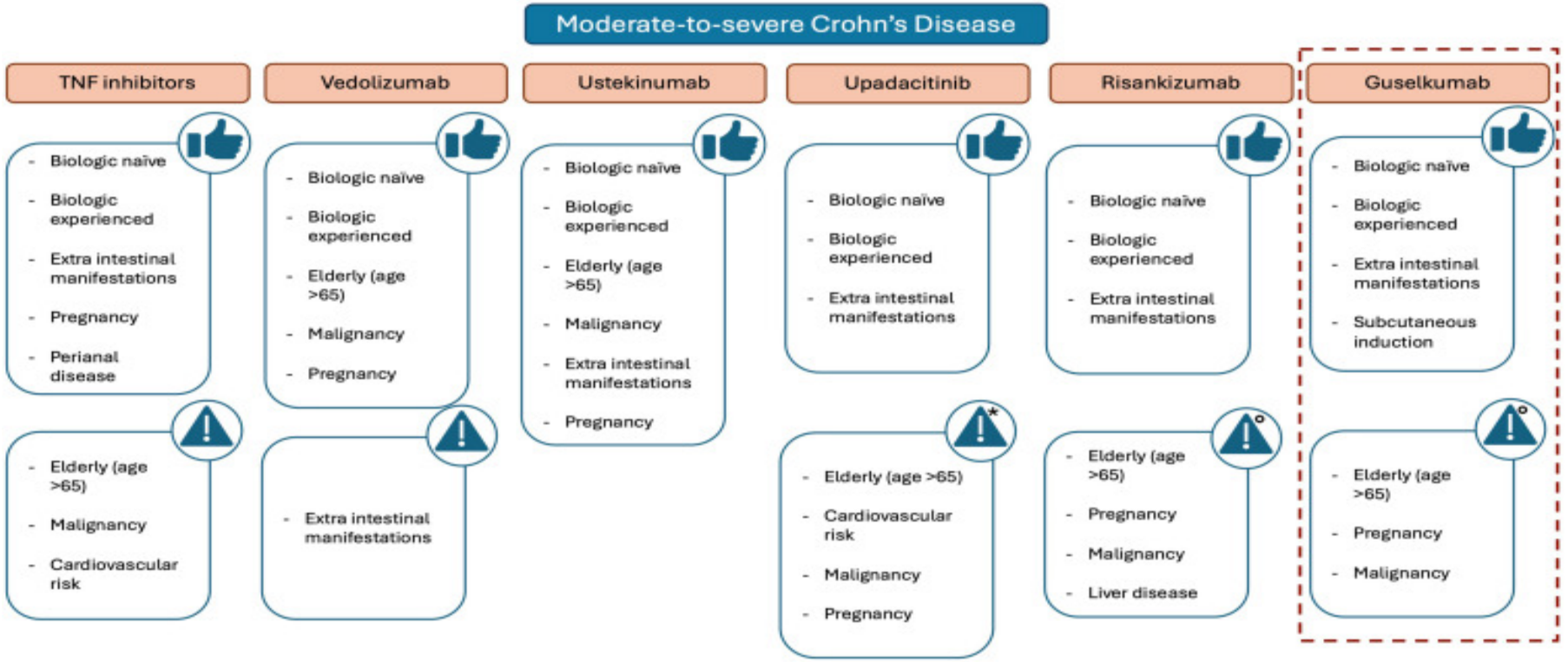
Ustekinumab vs Adalimumab for induction and maintenance in biologic naïve moderate to severe CD-SEAVUE





Sands B et al. Lancet. 2022;11:2200-2211.

Positioning of Medications



D'Amico F. Biologics. 2025 May 31;19:351-363.

Positioning in practice for CD

- Moderate disease
  - Start risankizumab – likely preferred over ustekinumab in TNF failures (SEQUENCE)
  - Upa for TNF failures
- Severe disease (perianal, fistulizing and stricturing)
  - Infliximab or adalimumab with or without IMM
  - TNF failures – upadacitinib (post hoc analysis in CD trial of 143 pts with fistula, 124 perianal and 19 enterocutaneous) higher percentage of fistula closure
- Perianal disease
  - Anti-TNF still preferred with thiopurine
  - Weaker data; upa >> IL12/23
- Special populations
  - Malignancy – risankizumab / ustekinumab / vedolizumab
  - Pregnancy – Avoid upadacitinib, S1P

Class	Baseline Testing	During Tx	Contraindications	Adverse Effects
Anti-interleukin (eg, ustekinumab, risankizumab, mirikizumab, guselkumab)	• TB • Viral hepatitis panel • Hepatic panel (risankizumab only) • Consider pregnancy test/discussion of family planning in women of childbearing potential (risankizumab only)	• Hepatic panel up to 12 weeks of treatment (risankizumab only) • Signs and symptoms of infection	• Live vaccines during treatment • Pregnancy (risankizumab) – can enroll into registry	Infections (upper respiratory, TB), PRES, headaches, arthralgia, abdominal site reactions, infusion/injection site reactions, hepatotoxicity (risankizumab only), anemia, arthropathy, urinary tract infection, skin cancer

Bhat S, Click B, Regueiro M. Safety and Monitoring of Inflammatory Bowel Disease Advanced Therapies. *Inflamm Bowel Dis*. 2023.

Class	Baseline Testing	During Tx	Contraindications	Adverse Effects
Janus Kinase (JAK) inhibitor (eg, tofacitinib JAK1,3, upadacitinib, JAK1)	• TB • Viral hepatitis • CBC - Not recommended if absolute lymphocyte count < 500 cells/mm^3, absolute neutrophil count < 1000 cells/mm^3, or Hgb level < 8 g/dL or decrease of more than 2 g/dL	• CBC, hepatic panel, every 3 months -lipid panel 4-8 wks tofa, 12 wks upa -Yearly skin exam	• Pregnancy/lactation • Live vaccines during treatment • Age ≥ 50 years old • Pre-existing cardiovascular history • Malignancy • VTE	Infections (upper respiratory tract infection, TB, **herpes zoster**), **hyperlipidemia**, increased blood creatinine phosphokinase, **acne**, neutropenia, hepatotoxicity, rash, MACE, VTE, malignancy

Bhat S, Click B, Regueiro M. Safety and Monitoring of Inflammatory Bowel Disease Advanced Therapies. *Inflamm Bowel Dis*. 2023.

ACG GUIDELINE *Highlights*

Management of Crohn's Disease in Adults

Concept and Content: Erica Duh, MD | **Reviewer:** Christina Y. Ha, MD, FACG

Diagnosis

- Consider clinical presentation as well as endoscopic, radiologic, histologic, and pathologic findings.
- Fecal calprotectin to differentiate inflammatory from noninflammatory (cutoff >50-100 ug/g)
- Routine endoscopic surveillance for CRC is recommended for colonic CD

Medical Management

Fistulizing Crohn's Disease

The following are recommended:

- Infliximab
- Adalimumab
- Antibiotics
- Upadacitinib
- Vedolizumab
- Ustekinumab

Surgical and Postoperative Crohn's Disease

- Recommend 6-12 month post-op colonoscopy to assess for early recurrent CD
- CD patients at high-risk for post-operative recurrence should consider starting advanced therapy shortly after resection.

Low Post-op Risk of Recurrence	High Post-op Risk of Recurrence
Observation	Anti-TNF Vedolizumab

What makes a patient HIGH risk?

- Active tobacco smoking
- Penetrating disease
- Prior CD resections

When to Refer to Surgery

- Intra-abdominal abscess >2 cm should be treated with drainage and antibiotics
- Patients with symptomatic fibrostenotic strictures or abdominal abscesses should be considered for surgery

Medical Management

EARLY initiation of advanced therapy is KEY for optimal outcomes in CD

		Induction	Maintenance	Comments
Mild to moderate disease	**Oral mesalamine**	⊘	⊘	
	Ileal release budesonide	✓	⊘	
Moderate to severe	**Oral corticosteroids** (Prednisone 40 mg daily for 1-2 weeks, with subsequent tapering)	✓	⊘	Think early advanced therapy for these patients
	Thiopurines (Azathioprine 2-2.5 mg/kg/day, Mercaptopurine 1-1.5 mg/kg/day)	⊘	✓	•TPMT testing before start •Given the adverse effect profile of thiopurine monotherapy (e.g. lymphoma, skin cancer), consider newer, safer agents for maintenance.
	Methotrexate (up to 25 mg 1x/week IM/SC)	⊘	✓	•↓ to 15 mg/wk @ 4 mo if steroid-free remission
	Anti-TNF agents (IV infliximab; SC adalimumab; SC certolizumab pegol)	✓	✓	•SC infliximab for maintenance only •Check TB, hepatitis B testing pre-treatment
	IV vedolizumab	✓	✓	SC vedolizumab for maintenance only
	Anti-IL 12/23 agents (Ustekinumab)	✓	✓	•RISA>> UST for anti-TNF experienced pt •GUS → SC or IV induction •MIRI, RISA, UST → IV induction •All use SC for maintenance
	Anti-IL 23 agents (Guselkumab; Mirikizumab; Risankizumab)	✓	✓	

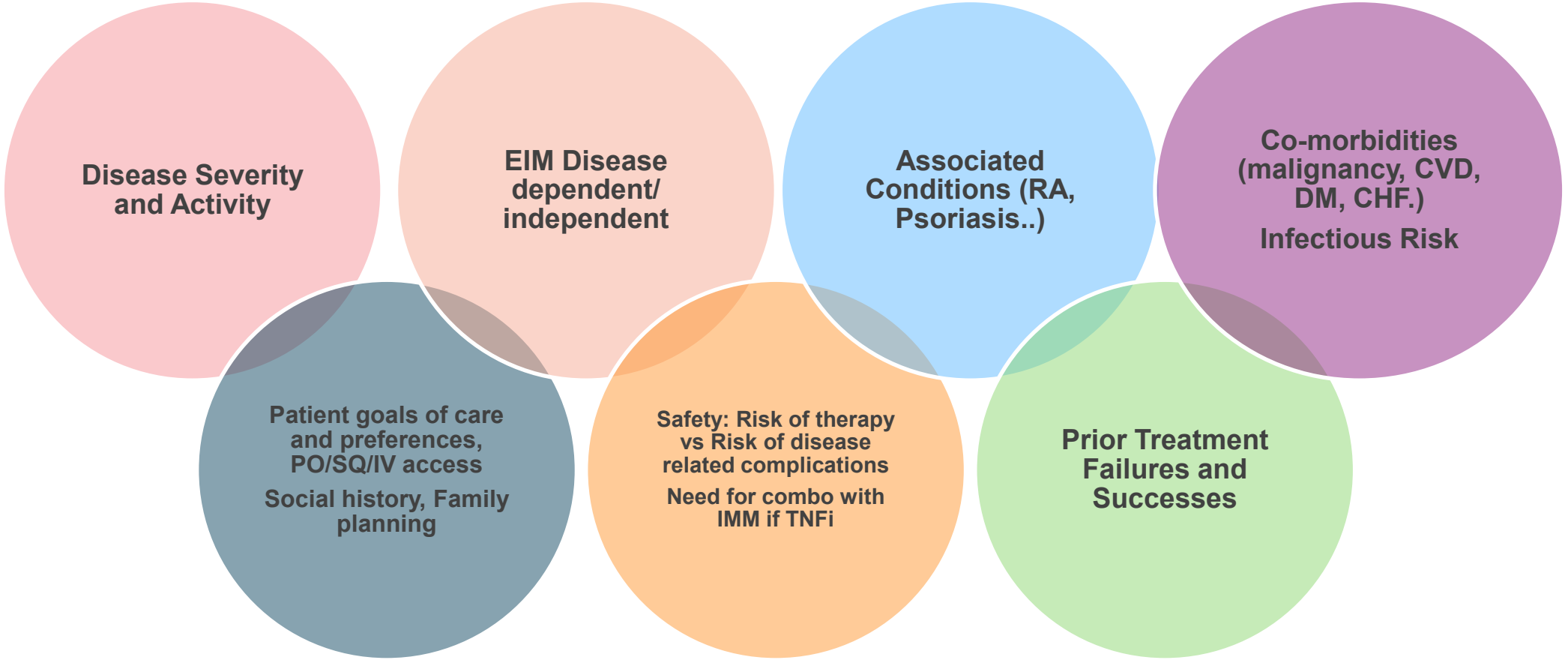
Sulfasalazine should be considered only for those with symptomatic mild colonic Crohn's disease

IV IFX + thiopurines >> immunomodulators or IV IFX alone in those who are naïve to those agents

Remember to address disease modifiers!

- NSAID use
- Cigarette smoking
- Management of stress, depression, and anxiety
- Diet

Individualize Therapy in IBD: Choosing the Right Medication for Each Patient



Slide Courtesy of Aline Charabaty, MD

Take Home Points

- Start treatment early after risk stratifying your patients
- Monitor disease state and modify medications incorporating objective parameters including intestinal bowel ultrasound
- Treatment should be based on co-existing medical problems and patient discussion
- Treatment with steroids for maintenance is never appropriate

Thank you @ReezwanaCMD