
2023
NCSCG
20TH ANNUAL
GI SYMPOSIUM

Clinical and Management Update in Inflammatory Bowel Disease

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Stanford University

Agenda

- Overview of current IBD medical therapies
- Getting to know the newer agents:
  - Anti-integrin new indication
  - IL-23
  - JAK-inhibitor
  - S1P receptor modulator
- Positioning of therapies

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The evolving landscape for IBD therapy

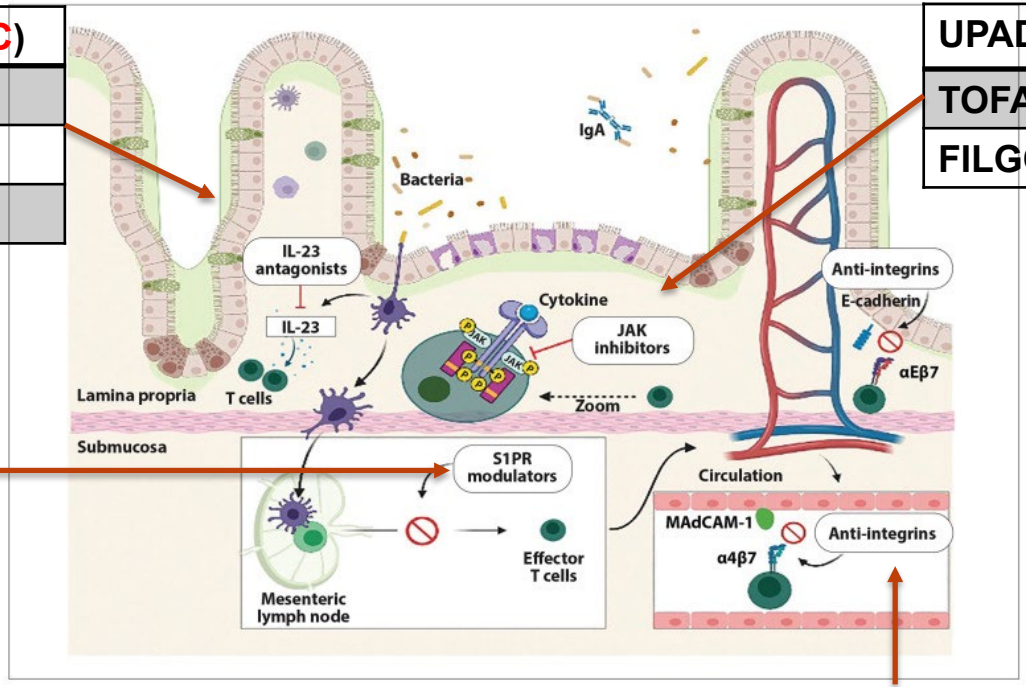
	Drug Class	Ulcerative Colitis	Crohn's Disease
Before 1998 — Conventional Therapy	**5-ASA**	Sulfasalazine Mesalamine(PO/Enema/Suppository)	——
	Corticosteroids	Prednisone Budesonide MMX Hydrocortisone (Foam/Enema/Supp)	Prednisone Budesonide CIR
	Immune Modulators	Azathioprine/Mercaptopurine Cyclosporine	Azathioprine/Mercaptopurine Methotrexate
1998 - 2018 — Biologics	**Anti-TNF**	Infliximab Adalimumab Golimumab	Infliximab Adalimumab Certolizumab Pegol
	Anti-Integrin	Vedolizumab	Vedolizumab
	Anti-IL-12/23 (p40)	Ustekinumab	Ustekinumab
	Anti-IL-23 (p19)	–	Risankizumab
2018-now — Targeted Small Molecules	**Janus kinase inhibitors**	Tofacitinib Filgotinib* Upadacitinib	Upadacitinib
	S1P Receptor Modulators	Ozanimod	——

***Approved outside US**
†Not yet approved
MMX: Multi-Matrix delivery system
CIR: Controlled Ileal Release

Novel Therapies According to Mechanism of Action

RISANKIZUMAB (CD / UC)
GUSELKUMAB
MIRIKIZUMAB
BRAZIKUMAB

UPADACITINIB (UC/CD)
TOFACITINIB (UC)
FILGOTINIB (UC)



OZANIMOD (UC)
ETRASIMOD (UC)

10 biosimilars

VEDOLIZUMAB (UC, CD)
ETROLIZUMAB (UC)

Santiago P, Braga Neto MB, Loftus EV. Gastroenterol Hepatol (NY) 2022; 18 (8): 453-365

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  - Anti-integrin: new indication
  - IL-23
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  - S1P receptor modulator
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Anti-integrin: Vedolizumab for mod to severe UC/ CD, and chronic pouchitis after IPAA for UC

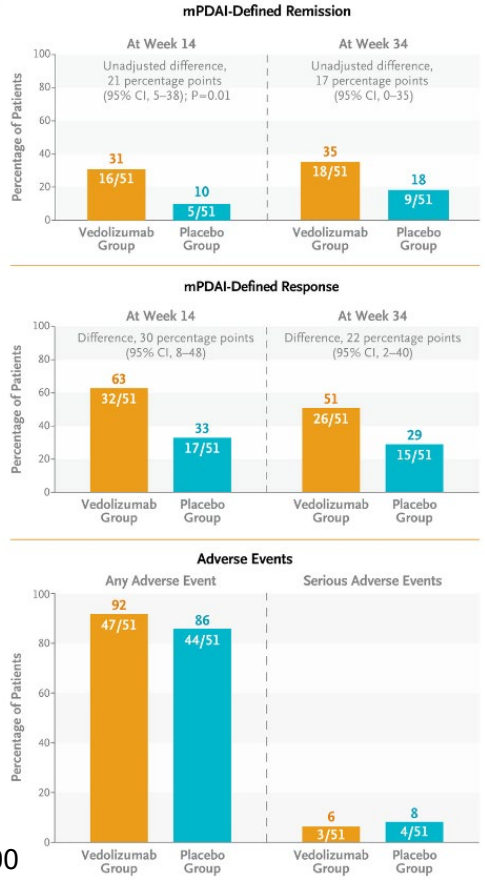
- Monoclonal antibody that targets α4β7 integrin primarily expressed in intestine, blocking pro-inflammatory cell recruitment to the gut
- First RCT double-blind PBO-controlled trial of biologic tx to show significant benefit in pouchitis.

Methods:

- Inclusion: aged 18-80 yo, IPAA for UC completed >1 yr prior to study, active chronic pouchitis
- Primary endpoint: mPDAI remission at wk 14
- Randomized to receive Vedolizumab 300 mg IV or PBO on day 1, wk 2, 6, 14, 22, 30. All received cipro for first 4 wks.

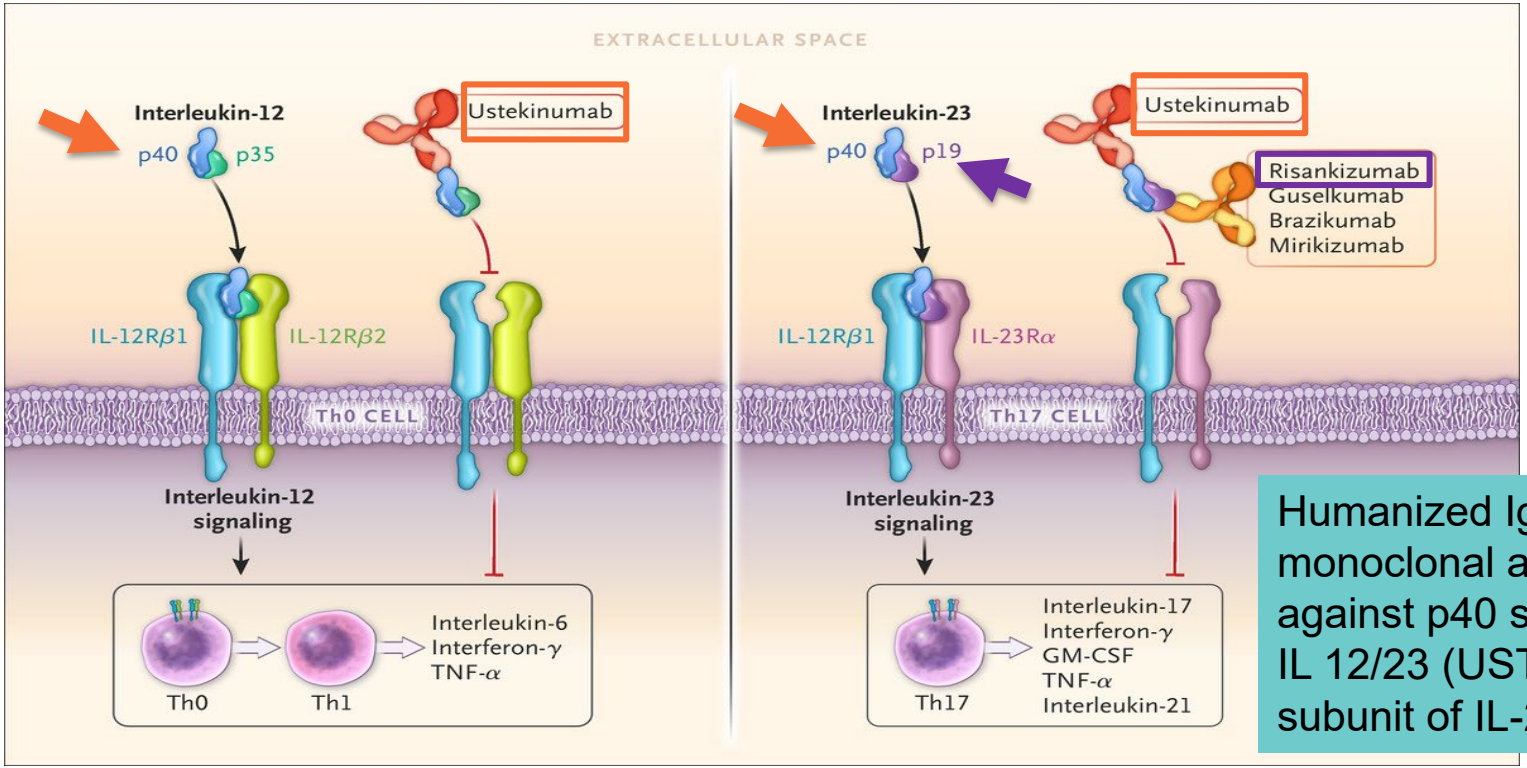
Conclusion:

- Vedo showed consistent treatment benefits over PBO across clinical, endoscopic, and histologic endpoints. Safety consistent with established profile.



Travis S et al. NEJM 2023; 388: 1191-1200

Anti-IL 12/23 Therapies: Ustekinumab, Risankizumab



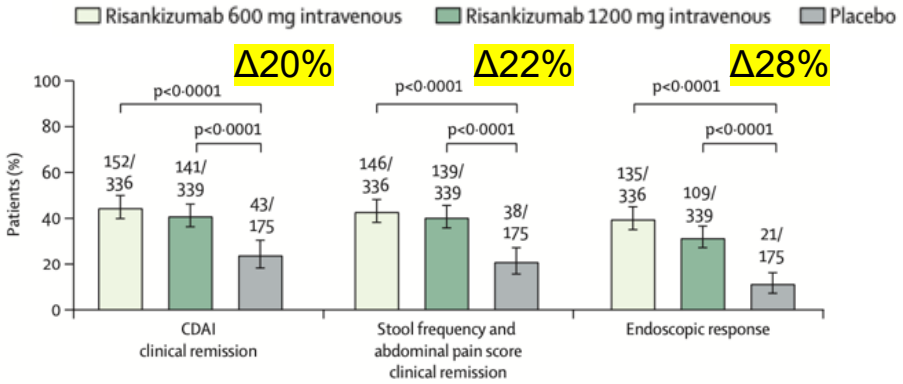
Humanized IgG1 monoclonal antibody against p40 subunit of IL 12/23 (UST); p19 subunit of IL-23 (RISA)

Th = T helper; TNF = tumor necrosis factor; GM-CSF = granulocyte-macrophage colony-stimulating factor.

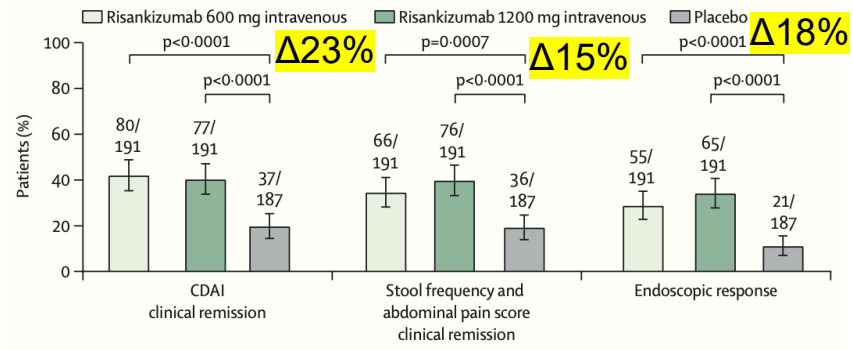
Baumgart DC, et al. *N Engl J Med*. 2021;385(14):1302-1315.

Anti IL-23 (p19): Risankizumab for mod to severe CD

Co-primary endpoints = clinical remission and endoscopic response



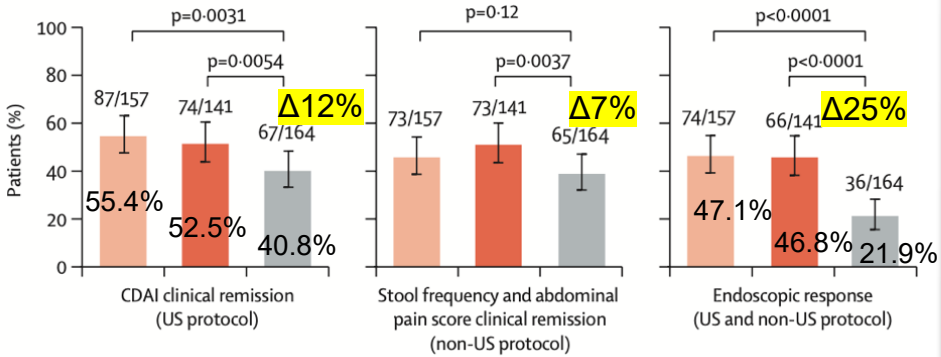
Co-primary endpoints at week 12 of ADVANCE (Non-Bio-IR and Bio-IR)



Co-primary endpoints at week 12 of MOTIVATE (Bio-IR)

D'Haens G et al. *Lancet*. 2022;399:2015-30.
Ferrante M et al. *Lancet*. 2022;399:2031-46.

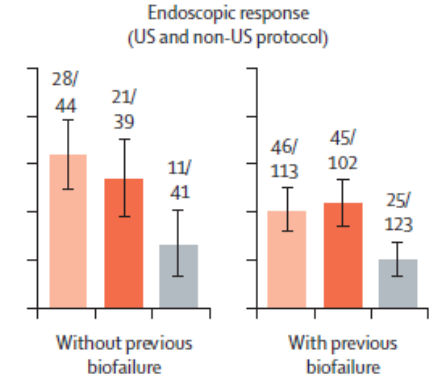
Anti IL-23 (p19): Risankizumab for mod to severe CD

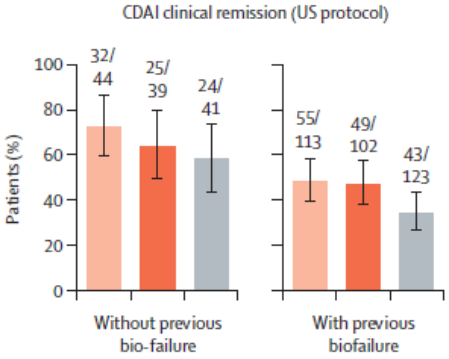


Co-primary endpoints at week 52 of FORTIFY

Risankizumab 180 mg
Risankizumab 360 mg
Withdrawal (subcutaneous placebo)

FORTIFY Results by Biologic Exposure, at week 52





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

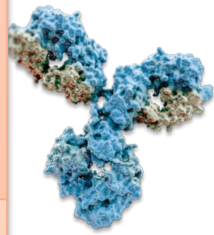
Anti IL-23 (p19): Risankizumab for mod to severe CD

Risankizumab CD Maintenance (FORTIFY) Adverse Events of Special Interest	Withdrawal (PBO SC) N = 184 (PYs = 160.4)	RZB 180 mg SC N = 179 (PYs = 169.3)	RZB 360 mg SC N = 179 (PYs = 166.4)
AE, exposure adjusted event rate		Events (E/100 PYs)	
CD	34 (12.2)	19 (11.2)	23 (13.8)
Serious Infection	8 (5.0)	5 (3.0)	10 (6.0)
Opportunistic infection (excluding TB or herpes zoster)	0	1 (0.6)	1 (0.6)
Herpes Zoster	1 (0.6)	2 (1.2)	0
Active TB	1 (0.6)	0	1 (0.6)
Adjusted MACEs	0	0	0
NMSC	1 (0.6)	0	0
Malignancies excluding NMSC	0	0	1 (0.6)
Serious hypersensitivity reactions	0	0	0
Adjusted anaphylactic reaction	0	0	0
Hepatic events	4 (2.5)	8 (4.7)	9 (5.4)
Injection site reactions	13 (8.1)	16 (9.5)	23 (13.8)

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

User's Guide for IL 12/23

	Ustekinumab (UST) / Risankizumab (RISA)	Considerations
Indications	CD (UST, RISA) and UC (UST) - Can be 1st biologic Plaque Psoriasis Psoriatic Arthritis	
Prior to use	TB Quantiferon, Hep serology CBC, LFT, Bilirubin, CRP, fecal calpro Role of combination with IMM less clear – can stop	- Immunogenicity: UST 0.77% RISA ~3-4%
Induction	UST: weight-based one IV dose @ week 0 <55 kg: 260 mg IV x 1 >55 kg to 85 kg: 390 mg IV x 1 <85 kg: 520 mg IV x 1 RISA: 600 mg IV @ week 0, 4, 8	- IV doses
Maintenance	UST: 90 mg SC @ week 8 , then q8 weeks RISA: 600 mg SC @ week 12, then q8 weeks	- SC doses - UST can increase to q4 weeks
Monitoring	- CBC, LFT, Cr - Check clinical symptoms in 4 weeks - Check objective markers (fecal calprotectin) in 4-8 weeks - Endoscopy / imaging in 6-12 months	- LFT at baseline and during induction - Therapeutic drug monitoring (TDM) less well established



JAK Inhibitors

Janus Kinase/Signal Transducer and Activator of Transcription

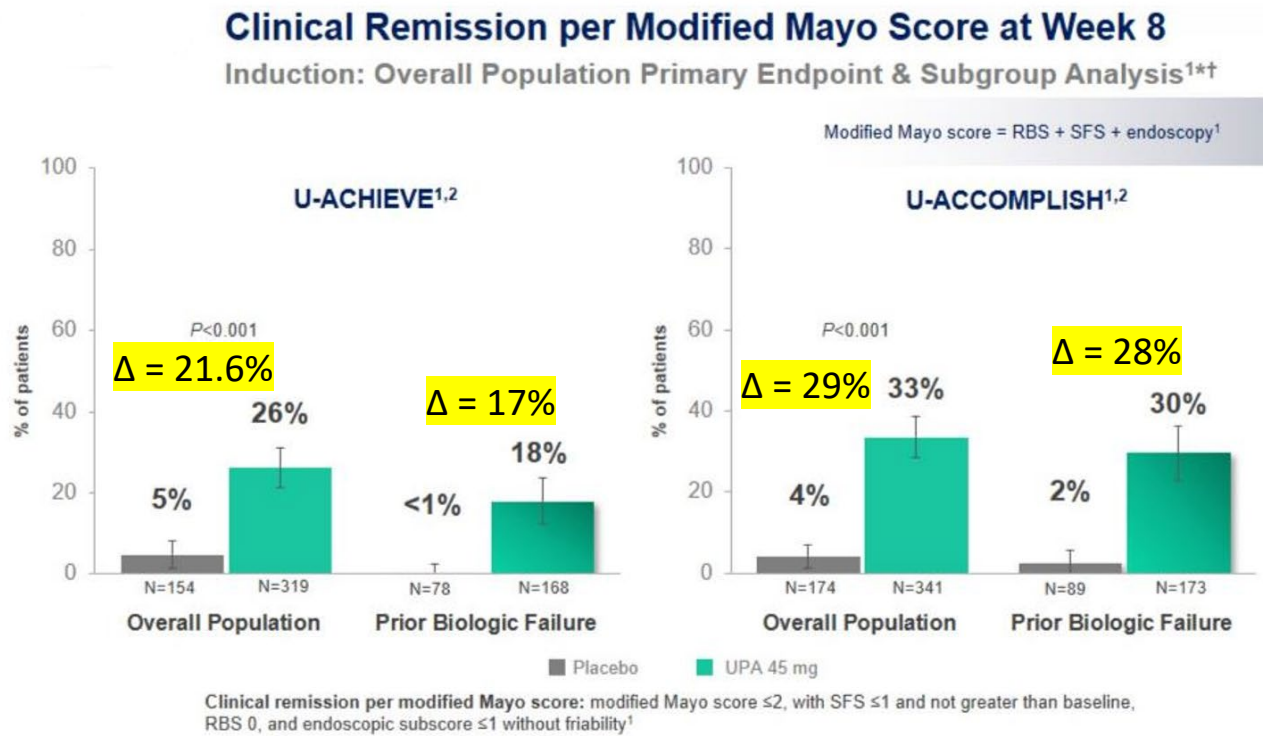
There are 4 JAK family members: JAK1, JAK2, JAK3, and Tyk2

Examples of cytokines that signal through JAK/STAT combinations

	TOFA	UPA	Filgot
JAK1, JAK2, TYK2	+	+	+
JAK1, JAK 3	+	+	+
JAK2, TYK2	+		
JAK2	+		

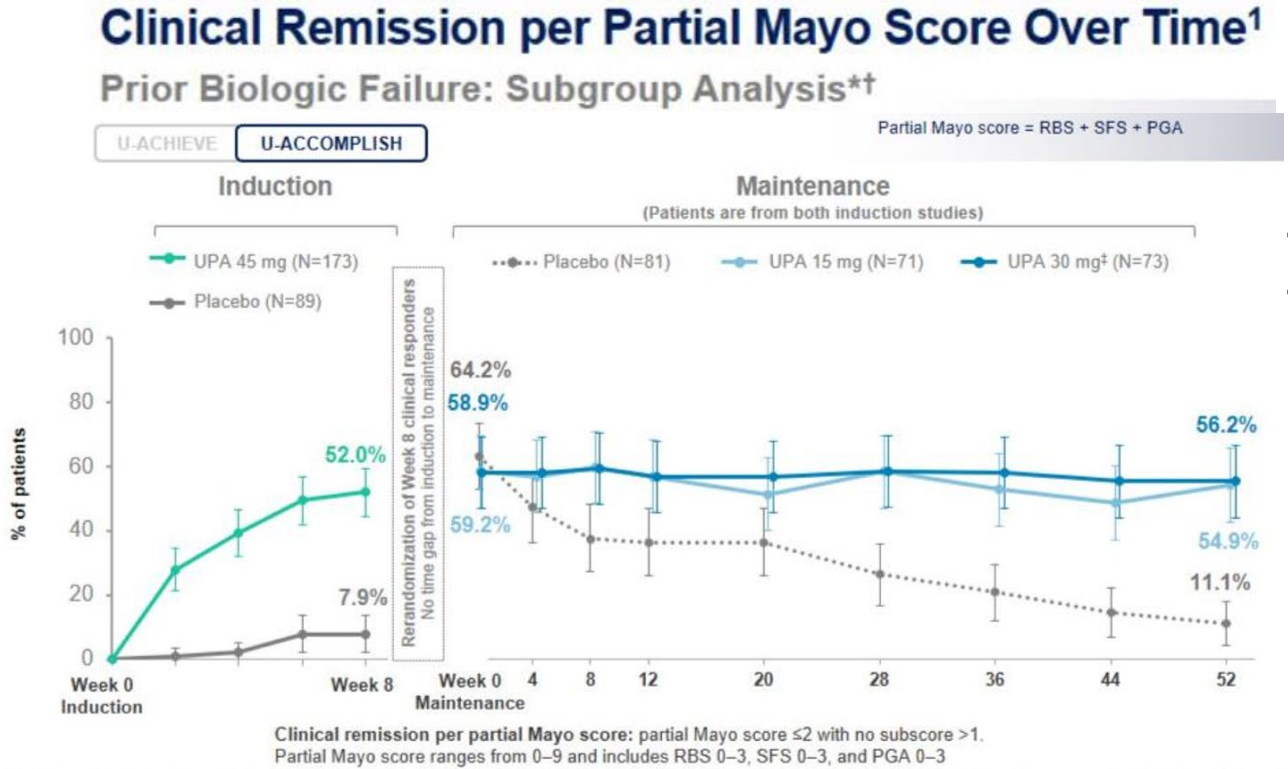
Hodge JA et al., *Clin Exp Rheumatol*. 2016;34(2):318-28.
O'Sullivan LA et al., *Mol Immunol* 2007; 44(10):2497-506.
Ghoreschi K et al., *Immunol Rev*. 2009;228(1):273-87.
Sanjabi S et al., *Curr Opin Pharmacol*. 2009;9(4):447-53.

JAK inhibitor: Upadacitinib for mod to severe UC



Danese et al. Lancet 2022; 399:2113-28.

JAK inhibitor: Upadacitinib for mod to severe UC



- Fast acting
- Early improvement (day 7): More likely to have clinical remission at week 8

Danese et al. Lancet 2022; 399:2113-28.

JAK inhibitor: Upadacitinib for mod to severe UC

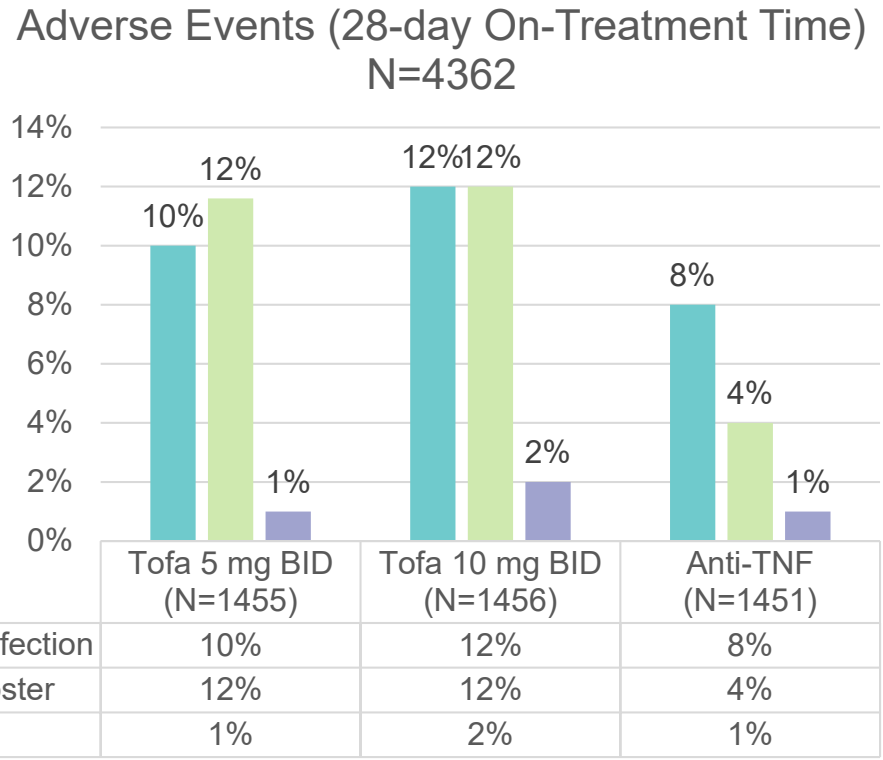
	Placebo (n=149)	Upadacitinib 15 mg once daily (n=148)	Treatment difference (95% CI)*	Upadacitinib 30 mg once daily (n=154)	Treatment difference (95% CI)*
Treatment-emergent adverse events					
Adverse events	113 (76%); 492·2	115 (78%); 304·2	2·4 (–7·0 to 11·8)	121 (79%); 304·9	3·1 (–6·2 to 12·3)
Serious adverse events	19 (13%); 27·5	10 (7%); 9·2	–6·1 (–13·0 to 0·7)	9 (6%); 6·7	–6·8 (–13·5 to –0·1)
Adverse events leading to discontinuation	17 (11%); 20·6	6 (4%); 5·9	–7·4 (–13·6 to –1·3)	10 (6%); 7·4	–4·8 (–11·4 to 1·8)
Death†	0	0	0	0	0
Most frequent adverse events (reported by ≥5% of patients in any treatment group across studies)					
Nasopharyngitis	15 (10%)	18 (12%)	..	22 (14%)	..
CPK elevation	3 (2%)	9 (6%)	..	13 (8%)	..
Worsening of ulcerative colitis	45 (30%)	19 (13%)	..	11 (7%)	..
URTI	6 (4%)	7 (5%)	..	9 (6%)	..
Acne	6 (4%)	4 (3%)	..	6 (4%)	..
Arthralgia	15 (10%)	9 (6%)	..	5 (3%)	..
Headache	6 (4%)	4 (3%)	..	5 (3%)	..
Anaemia	6 (4%)	7 (5%)	..	1 (<1%)	..

Danese et al. Lancet 2022; 399:2113-28.

ORAL Surveillance: Specifically Designed Trial to Assess Tofacitinib Safety (MACE and Malignancy)

- RCT open-label follow-up of RA patients older than 50 years old with at least 1 additional CV risk factor
- Increased risks:
  - MACE : HR 1.33 (95% CI 0.91 - 1.94)
  - Cancers: HR 1.48 (95% CI 1.04 - 2.09)

Black Box Warning for:
- Serious Infections
- Mortality
- Malignancy
- MACE
- Thrombosis



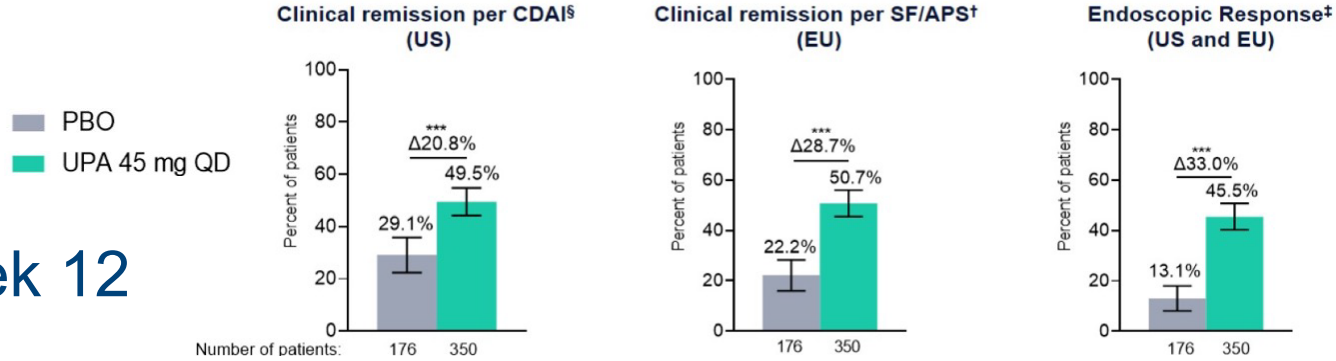
	Tofa 5 mg BID (N=1455)	Tofa 10 mg BID (N=1456)	Anti-TNF (N=1451)
Serious Infection	10%	12%	8%
Herpes zoster	12%	12%	4%
VTE	1%	2%	1%

Anti-TNF = adalimumab or etanercept

Ytterberg, et al. N Engl J Med 2022

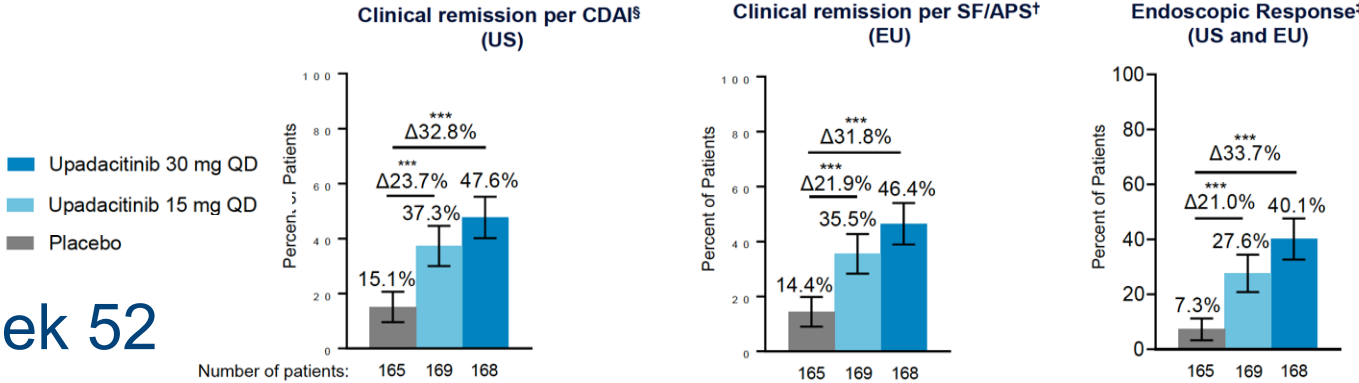
JAK inhibitor: Upadacitinib for mod to severe CD

Week 12



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

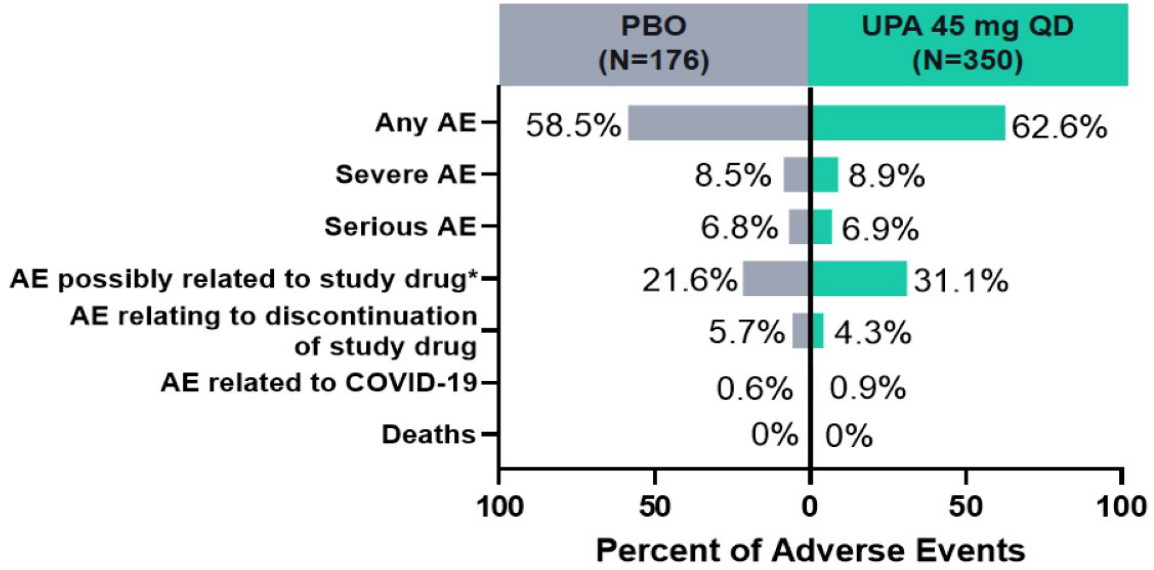
Week 52



Panes J, et al. *Am. J. Gastroenterol.* 2022;17(s8).

JAK inhibitor: Upadacitinib for mod to severe CD

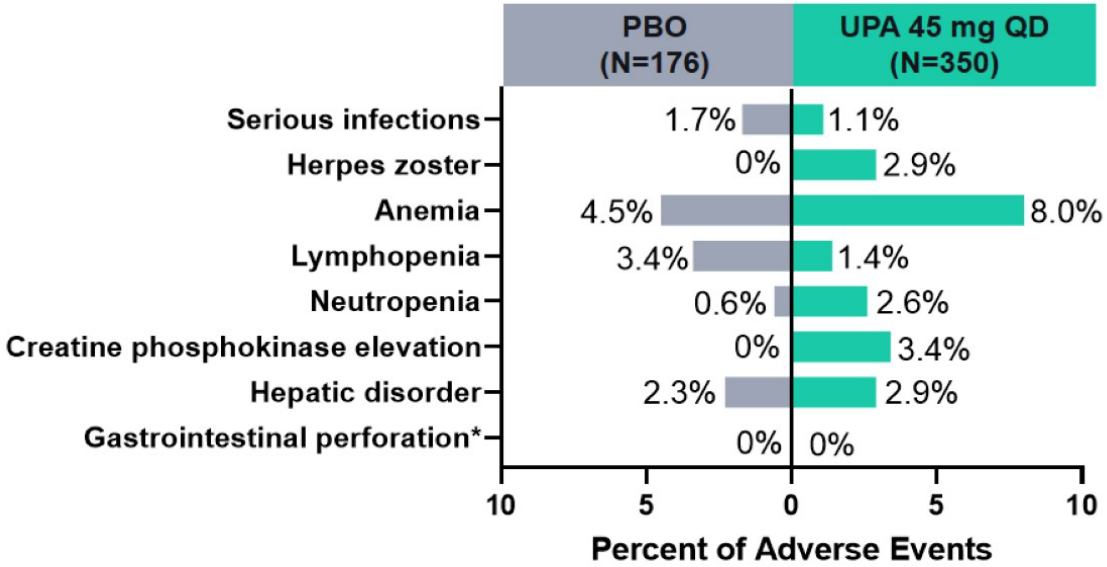
Treatment-Emergent Adverse Events (AEs)



* As assessed by investigator

JAK inhibitor: Upadacitinib for mod to severe CD

Adverse Events of Special Interest (AESI)



No opportunistic infections (excluding tuberculosis and herpes zoster), tuberculosis, renal disorders, adjudicated cardiovascular or venous thromboembolic events, or cancer of any kind were observed in either group.

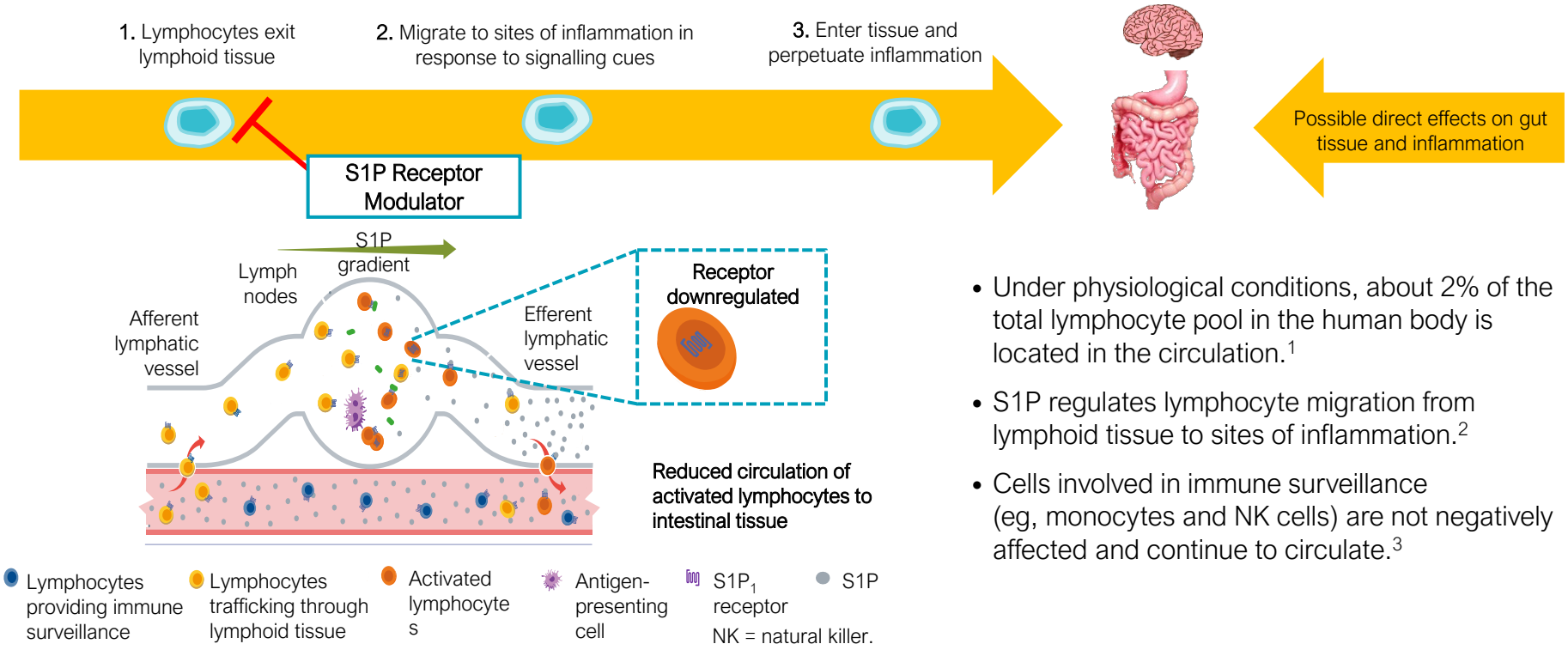
Anemia of AESI is based on CMQ search, which includes other preferred terms, in addition to the preferred term "anaemia".
*One event of adjudicated gastrointestinal perforation (intestinal perforation) was reported in a patient who was a clinical non-responder to placebo and was on UPA 45 mg QD in the extended treatment period.

Users' Guide for JAK Inhibitors

	Tofacitinib / Upadacitinib	Considerations
Indications	Mod-severe UC (TOFA, UPA) ; Mod-severe CD (UPA)	must have prior TNF failures
Prior to use	TB QuantiFERON, Hep serology CBC, LFT, Bilirubin, CRP, fecal calpro, lipid panel Vaccinate against herpes zoster (age >18) Assess VTE /MACE risk factors Stop immunomodulator	 Black box warning Caprini score for VTE No immunogenicity
Induction	Tofacitinib 10 mg PO BID for **8** -16 wks Upadacitinib 45 mg PO daily for **8**-16 wks (UC)/ **12** wks (CD)	Faster onset Consider steroid sparing
Maintenance	Tofacitinib 5 mg or 10 mg PO BID Upadacitinib 15 or 30 mg PO BID	Higher doses more effective Decrease dose for moderate renal/hepatic impairment
Monitoring	- CBC at 4-8 wks then q3 months for Tofa - LFT at wk 8-12, then q3-6 months - Lipids at wk 4-8 for Tofa, wk 12 for Upa, then q12 months - Pregnancy/ Conception - Check clinical symptoms in 4 wks - Check objective markers (fecal calprotectin) in 4-8 wks - Endoscopy / imaging in 6-12 months	No TDM

Do not use if:
-ANC < 500, Hb < 8
-Severely elevated LFT
-Severe renal impairment (eGFR<15)
-Severe hepatic impairment (CPT C)
-combined with strong CYP3A4 inhibitors (e.g. ketoconazole, clarithromycin)

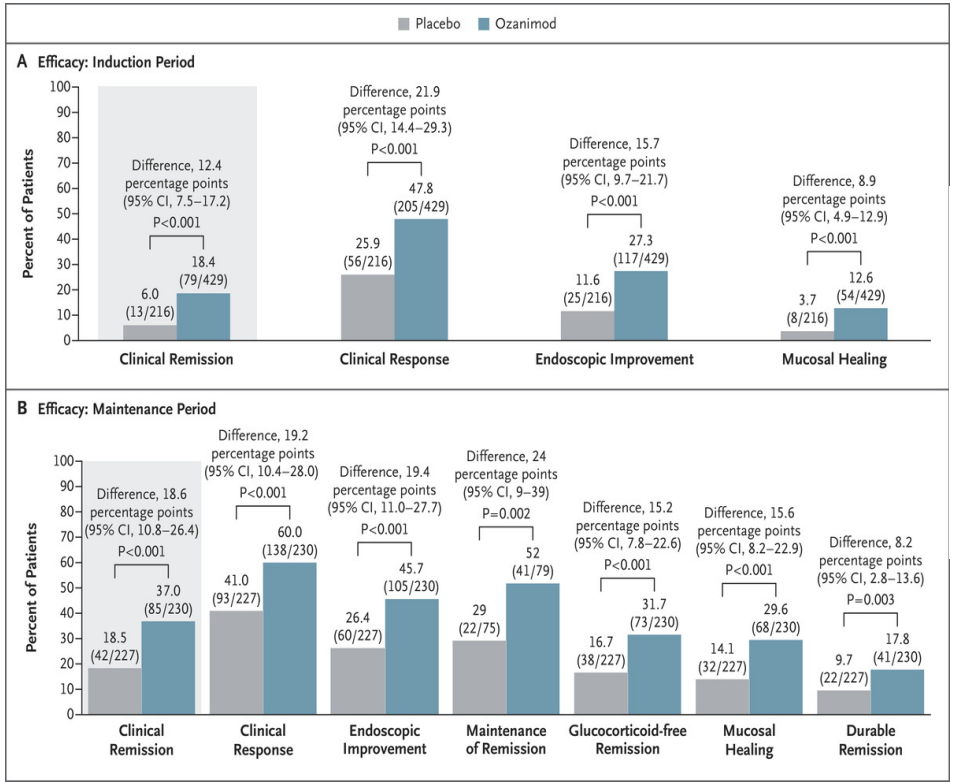
S1P Receptor Modulator Mechanism of Action



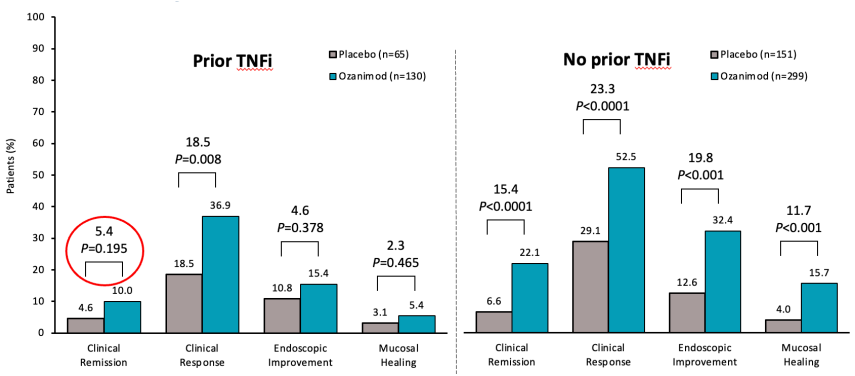
- Under physiological conditions, about 2% of the total lymphocyte pool in the human body is located in the circulation.[1]
- S1P regulates lymphocyte migration from lymphoid tissue to sites of inflammation.[2]
- Cells involved in immune surveillance (eg, monocytes and NK cells) are not negatively affected and continue to circulate.[3]

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

S1P receptor mod: Ozanimod for mod to severe UC



TRUENORTH Week 10 Induction



WJ Sandborn et al. N Engl J Med 2021;385:1280-1291.

User's Guide for Ozanimod – mod to severe UC

Baseline assessment	Test	Specific Advice
Cardiac	ECG, blood pressure Check drug history for medications that may slow heart rate or AV conduction	Contraindicated in patients who in the last 6 months have had • myocardial infarction • unstable angina, stroke • transient ischemic attack • Decompensated, Class III or IV heart failure Or have • Mobitz type II second degree or third-degree atrioventricular block • sick sinus syndrome • sinoatrial block (unless functional pacemaker)
Full blood count	Lymphocyte count	Patients with counts <0.8x10^{9}/L excluded from True North Mean 50% reduction in total lymphocyte count after initiation
Liver function tests	AST, ALT, bilirubin	5% patients develop transaminitis >3x ULN
Ophthalmic assessment	Fundoscopy	Required in patients with history of diabetes, uveitis or macular edema
Virology and TB	Standard virology screen including VZV serology TB QuantiFERON	Consider vaccination if VZV IgG- (live vaccines require administration 1 month prior to initiation) Herpes zoster – commonest opportunistic infection
Other contraindications	Severe untreated sleep apnea, monoaminoxidase inhibitor use	
Dosing Titrating	Titrate once daily dose to maintenance dose at one week: 0.25 mg days 1-4, 0.5 mg days 5-7, then 1 mg OD	

Safety: infections, bradycardia, atrioventricular conduction delays, liver injury, and macular edema

[prescribing information]

Agenda

- Overview of current IBD medical therapies
- Getting to know the newer agents:
  - Anti-integrin – new indication
  - IL-23
  - JAK-inhibitor
  - S1P receptor modulator
- Positioning of therapies

Factors in Treatment and Management Decisions

DRUG

Efficacy

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

Safety

Infection
Cancer
Specific concerns by agent or mechanism

PATIENT

Individual Characteristics

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

Disease Characteristics

CD vs. UC
Disease behavior/complication
Disease severity
Early vs. late
Extraintestinal manifestations
Prior treatment success or failure

EIMs = extraintestinal manifestations; TDM = therapeutic drug monitoring

Slide courtesy of Anita Afzali, MD

ACG Clinical Guideline: Management of Crohn's Disease in Adults

Lichtenstein, Gary R MD, FACG[1]; Loftus, Edward V MD, FACG[2]; Isaacs, Kim L MD, PhD, FACG[3]; Regueiro, Miguel D MD, FACG[4]; Gerson, Lauren B MD, MSc, MACG (GRADE Methodologist)[5,†]; Sands, Bruce E MD, MS, FACG[6]

Author Information

American Journal of Gastroenterology: April 2018 - Volume 113 - Issue 4 - p 481-517
doi: 10.1038/ajg.2018.27

ACG Clinical Guideline: Ulcerative Colitis in Adults

David T. Rubin, MD, FACG[1], Ashwin N. Ananthakrishnan, MD, MPH[2], Corey A. Siegel, MD, MS[3], Bryan G. Sauer, MD, MSc (Clin Res), FACG (GRADE Methodologist)[4] and Millie D. Long, MD, MPH, FACG[5]

ECCO Guidelines on Therapeutics in Ulcerative Colitis: Medical Treatment FREE

Tim Raine ✉, Stefanos Bonovas, Johan Burisch, Torsten Kucharzik, Michel Adamina, Vito Annese, Oliver Bachmann, Dominik Bettenworth, Maria Chaparro, Wladyslawa Czuber-Dochan ... Show more

Journal of Crohn's and Colitis, Volume 16, Issue 1, January 2022, Pages 2–17,

ECCO Guidelines on Therapeutics in Crohn's Disease: Medical Treatment FREE

Joana Torres, Stefanos Bonovas, Glen Doherty, Torsten Kucharzik, Javier P Gisbert, Tim Raine, Michel Adamina, Alessandro Armuzzi, Oliver Bachmann, Palle Bager ... Show more

Author Notes

Journal of Crohn's and Colitis, Volume 14, Issue 1, January 2020, Pages 4–22,

CLINICAL PRACTICE GUIDELINE | VOLUME 160, ISSUE 7, P2496-2508, JUNE 01, 2021

AGA Clinical Practice Guidelines on the Medical Management of Moderate to Severe Luminal and Perianal Fistulizing Crohn's Disease

Joseph D. Feuerstein • Edith Y. Ho • Eugenia Shmidt • Harminder Singh • Yngve Falck-Ytter • Shanaz Sultan • Jonathan P. Terdiman •
on behalf of the American Gastroenterological Association Institute Clinical Guidelines Committee • Show less

DOI: https://doi.org/10.1053/j.gastro.2021.04.022 • Check for updates

AGA Clinical Practice Guidelines on the Management of Moderate to Severe Ulcerative Colitis

Joseph D. Feuerstein • Kim L. Isaacs • Yecheskel Schneider • ... Yngve Falck-Ytter • Siddharth Singh •
on behalf of the AGA Institute Clinical Guidelines Committee • Show all authors

Published: January 13, 2020 • DOI: https://doi.org/10.1053/j.gastro.2020.01.006 • Check for updates

- Few head-to-head trials (VARSITY, SEAVUE)
- Comparative effectiveness of agents largely inferred from indirect comparisons from network meta-analyses

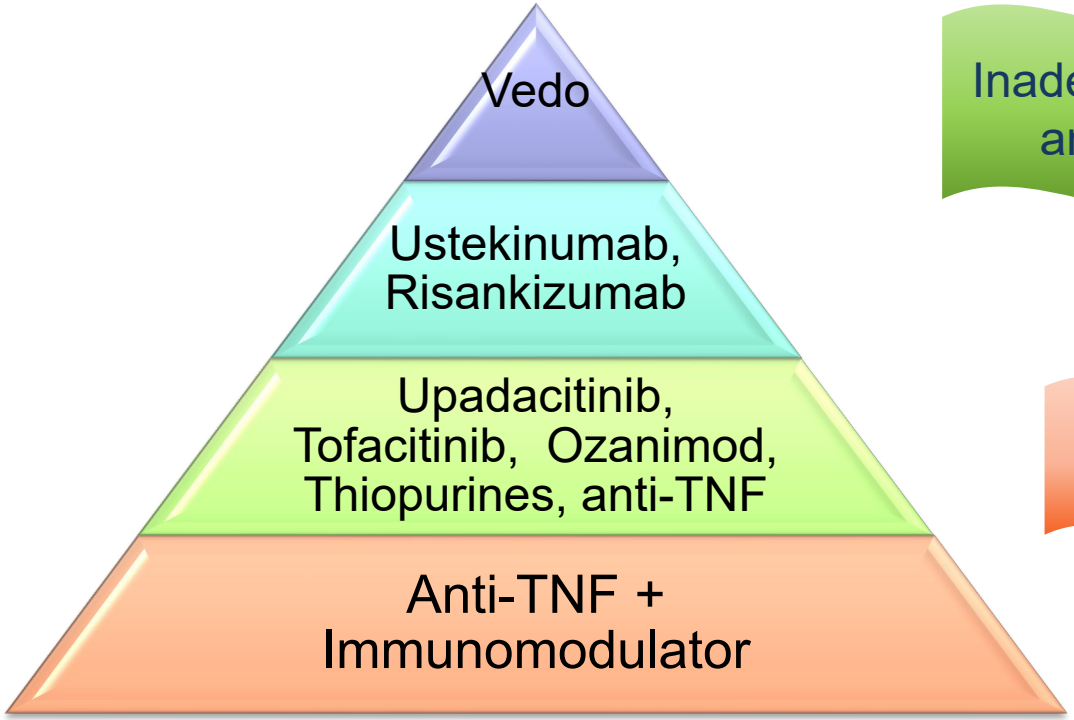
Summary of Current IBD Advanced Therapies

	TNFi (IFX, AZA, CTZ, GOL)	Anti-Integrin (VEDO)	Anti-IL 23 ± 12 (UST, RISA)	JAK inhibitor (TOFA, UPA)	S1P (OZA)
Indication	UC, CD	UC, CD, chronic pouchitis	UC, CD	UC	UC
Admin	IV, SQ	IV (SC coming?)	IV then SQ	Oral	Oral
Efficacy	Fast onset Best with IMM	Better in TNF-naïve	Fast onset For TNFi-naïve and failure	Rapid onset For TNFi-failure	Better in TNF-naïve
Immunogenicity	↑	↓	↓	↓	↓
EIM	+ perianal disease	-	Psoriasis PsA	RA, AS, PsA Psoriasis pcJIA, Eczema	Multiple Sclerosis
Safety	Infection Lymphoma	Excellent (Gut-selective)	Excellent	Herpes zoster MACE, VTE (RA>> UC)	↓HR after first dose, ↓ Lymphocytes)

My Safety Pyramid of Current IBD meds

Safest

Least Safe



STEROIDS

Inadequate treatment is an adverse event

Surgery is an option

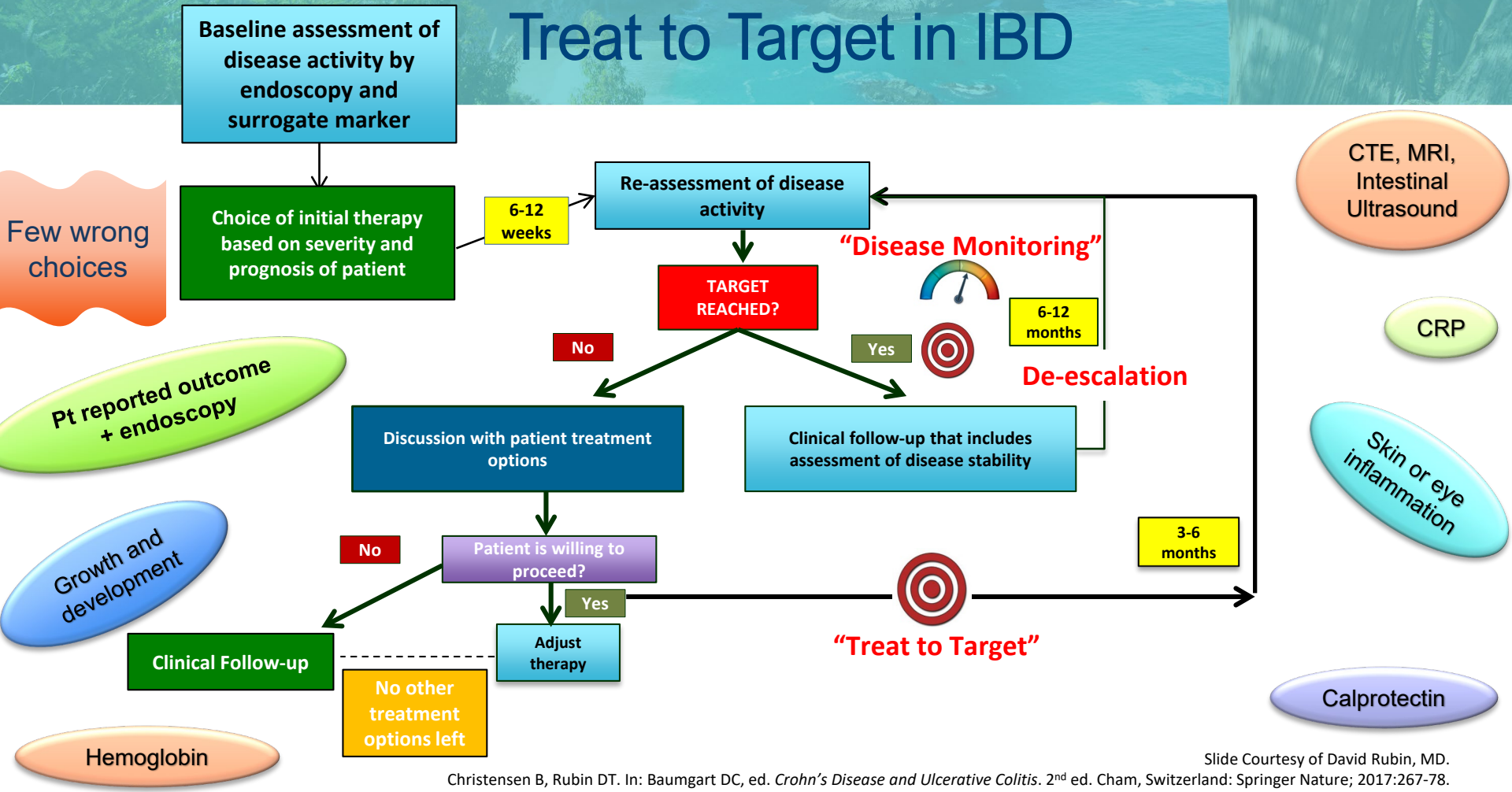
Is selectivity = safer?

Which one to choose as 1st line?

IBD type	General population	Risk adverse (>60 yo, cancer, infection)	2nd line (failed anti-TNF)
UC Severe/hospitalized	IFX (10 mg/kg) + IMM (MTX in young males)		UPA>TOFA (UPA fastest onset; but more data needed for inpt)
UC mod-severe	TNFi or VEDO or OZA or UST	VEDO or UST > OZA (no sig cardiac dx) or UPA or IFX	UPA > TOFA or UST > VEDO
CD mod-severe	TNFi or UST or RISA > VEDO	UST or RISA > VEDO	Primary non-response: UPA or UST or RISA > VEDO Secondary non-response: ADA/IFX or UPA or UST
CD with perianal disease	IFX + IMM +/- antibiotics		
Chronic pouchitis	VEDO		

Consider EIM

Treat to Target in IBD

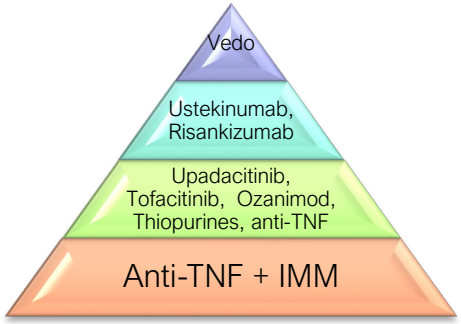


Slide Courtesy of David Rubin, MD.

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

Summary

- FDA approved agents for mod to severe UC: 5-ASA, thiopurines, steroids, anti-TNF, VEDO, UST, TOFA, UPA, OZA
- FDA approved agents for mod to severe CD: thiopurines, steroids, VEDO, UST, RISA, UPA
- VEDO can be used for chronic pouchitis
- TOFA /UPA are used after anti-TNF failure; UPA has fairly rapid onset of action.
- OZA have modest efficacy, no boxed warning
- More agents coming down the pipeline plus 10 biosimilars
- Positioning of therapy depends on drug and patient factors
- Develop a monitoring strategy to treat to an appropriate target



Thank you

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Questions:

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