

Positioning Advanced Therapies for Ulcerative Colitis

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Disclosures

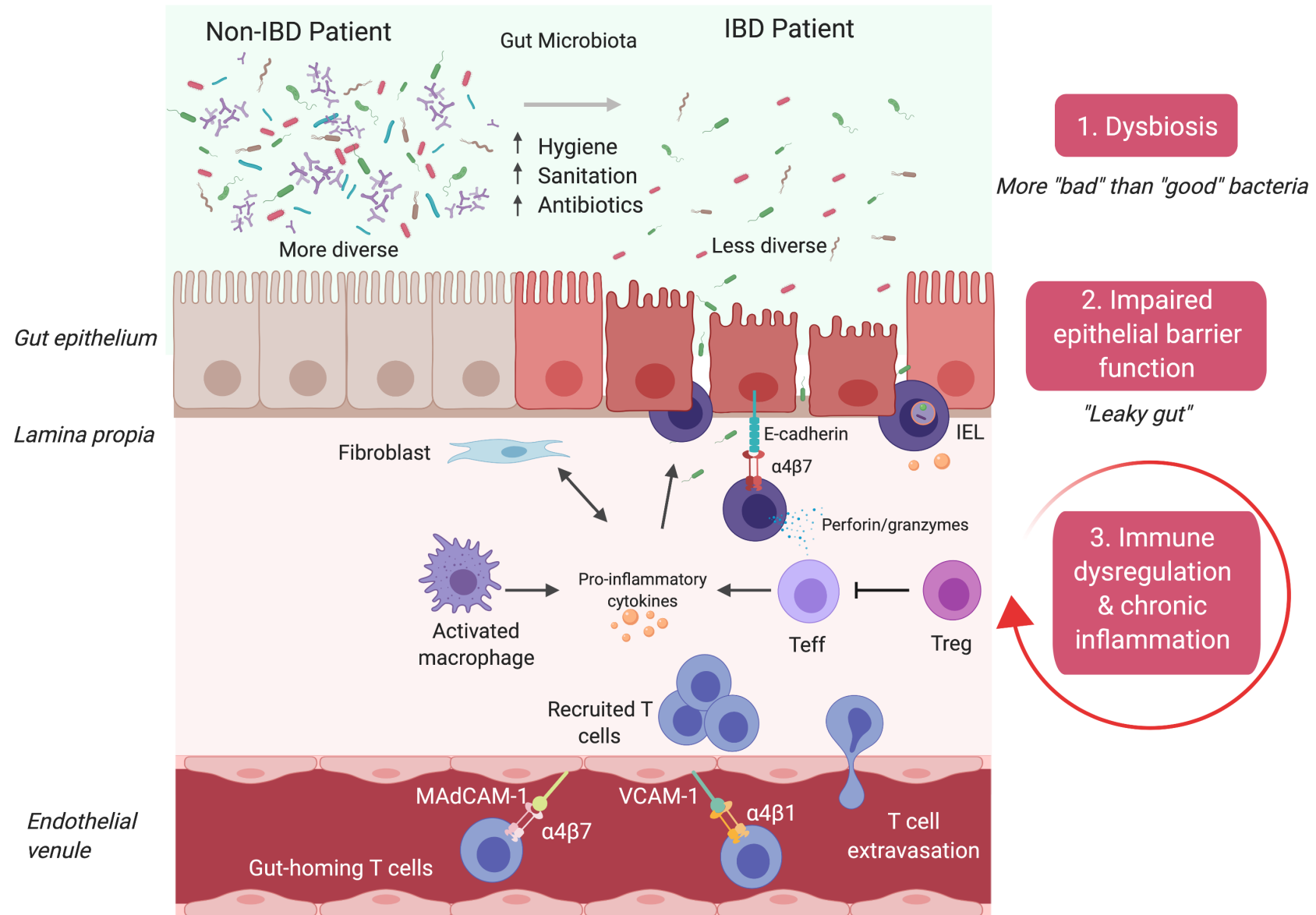
Consultant/Advisory Boards:

- Abbvie
- Allergan
- Amgen
- BMS
- Celgene
- Genentech
- Gilead
- Janssen
- Lilly
- Pfizer
- Prometheus
- Salix
- Seres
- Takeda
- UCB

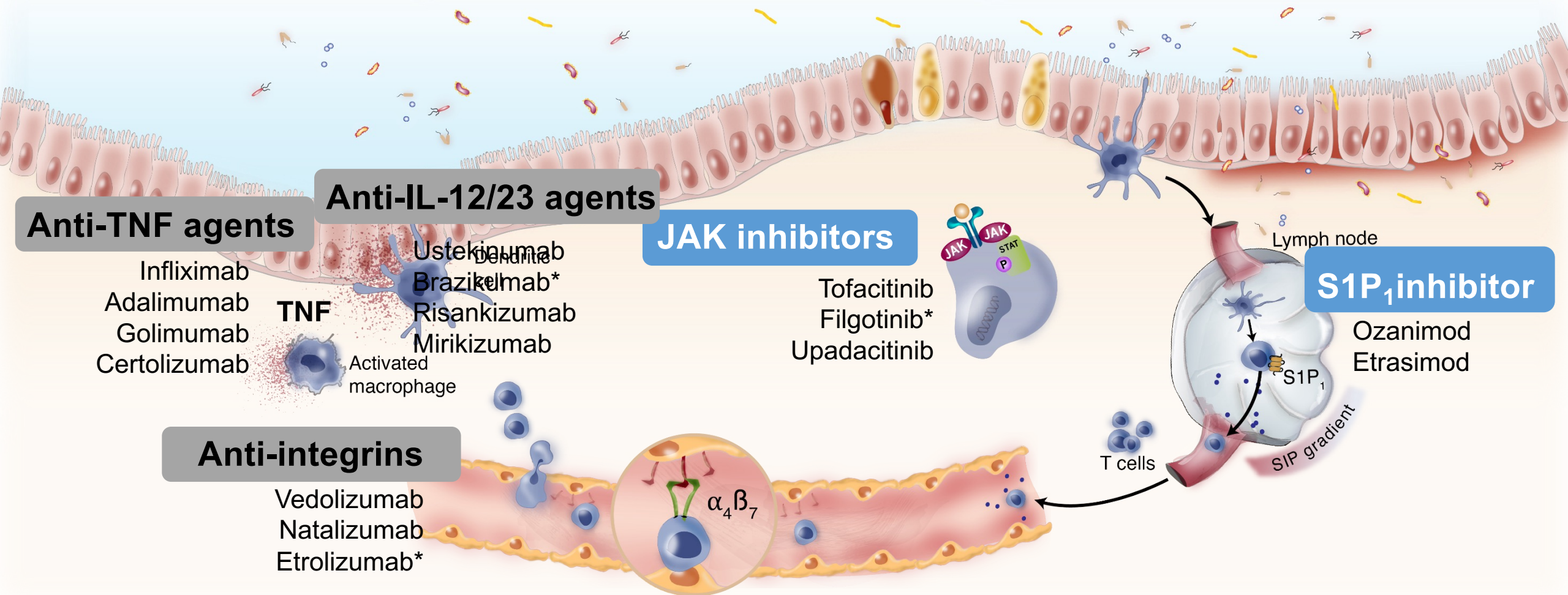
Educational Companies

- CMEOutfitters
- Cornerstones
- GiHF
- IBDRemedy
- Imedex
- UpToDate
- Vindico

Pathogenesis of IBD is Multifactorial



Current and Emerging Strategies for IBD



FDA-Approved Targeted Therapies for IBD

Class	CD	UC
TNF inhibitor	Adalimumab ¹ Certolizumab ² Infliximab ³	Adalimumab ¹ Golimumab ⁸ Infliximab ³
IL-12/IL-23 inhibitor	Ustekinumab ⁴ Risankizumab ⁵	Ustekinumab ⁴ Mirikizumab
Integrin inhibitors	Natalizumab ⁶ Vedolizumab ⁷	Vedolizumab ⁷
JAK inhibitors	Upadacitinib	Tofacitinib ⁹ Upadacitinib ¹⁰
S1P receptor modulators	—	Ozanimod ¹¹ Etrasimod

1. Humira (adalimumab) Prescribing Information. <https://www.rxabbvie.com/pdf/humira.pdf>. 2. Cimzia (certolizumab pegol) Prescribing Information. https://www.cimzia.com/themes/custom/cimzia/docs/CIMZIA_full_prescribing_information.pdf. 3. Remicade (infliximab) Prescribing Information. <http://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/REMICADE-pi.pdf>. 4. Stelara (ustekinumab) Prescribing Information. <http://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/STELARA-pi.pdf>. 5. Skyrizi (risankizumab-rzaa) Prescribing Information. https://www.rxabbvie.com/pdf/skyrizi_pi.pdf. 6. Tysabri (natalizumab) Prescribing Information. https://www.tysabrihcp.com/content/dam/commercial/tysabri/hcp/en_us/pdf/tysabri_prescribing_information.pdf. 7. Entyvio (vedolizumab) Prescribing Information. <https://general.takedapharm.com/ENTYVIOPI>. 8. Simponi (golimumab) Prescribing Information. <http://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/SIMPONI-pi.pdf>. 9. Xeljanz (tofacitinib) Prescribing Information. <http://labeling.pfizer.com/ShowLabeling.aspx?id=959>. 10. Rinvoq (upadacitinib) Prescribing Information. https://www.rxabbvie.com/pdf/rinvoq_pi.pdf. 11. Zeposia (ozanimod) Prescribing Information. https://packageinserts.bms.com/pi/pi_zeposia.pdf.

Timeline of IBD Therapies

Crohn's Disease

Sulfasalazine

Thiopurines

Infliximab
(1998)

Adalimumab
(2007)

Natalizumab
(2008)

Certolizumab
(2009)

Vedolizumab
(2014)

Ustekinumab
(2016)

Risankizumab
(2022)

Upadacitinib
(2023)

1950

1960

1970

1980

1990

2000

2010

2020

Sulfasalazine

Thiopurines

Infliximab
(2005)

Adalimumab
(2012)

Golimumab
(2013)

Vedolizumab
(2014)

Ustekinumab
(2019)

Tofacitinib
(2018)

Ozanimod
(2021)

Upadacitinib
(2022)

Etrasimod
(2023)

Mirikizumab
(2023)

Ulcerative Colitis

IBD Landscape: *personalizing* the choice of advanced therapy

TNFi

(IFX, ADA, CTZ, GOL)

- IV and SQ options
- Rapid onset of action
- Best with IMM (SONIC)
- +EIMs/perianal disease
- Immunogenicity
- Infection risk
- Lymphoma risk (with IMM)

Anti Integrin

(VDZ)

- IV (SQ now in USA)
- Better results in TNFi naïve
- Low immunogenicity
- Gut-selective with excellent safety profile

Anti IL23+/-12

(UST, RISA, MIRI)

- IV then SQ
- Fast onset of action
- Efficacy in TNFi naïve and failure
- Low immunogenicity
- +Psoriasis, PsA
- Excellent safety profile
- Bowel urgency ↓ MIRI

JAKi

(TOFA, UPA)

- Oral, UC and CD (UPA)
- Rapid onset of action
- Efficacy in TNFi naïve & failure
- No Immunogenicity
- +EIMs (RA, Psoriasis, AtDerm)
- Herpes Zoster
- MACE & VTE (RA >> UC)

S1P

(OZA, ETRA)

- Oral, UC only
- Better results in TNFi naïve
- No Immunogenicity
- +Multiple Sclerosis
- Good Safety
- Initial dose titration: 1st dose HR ↓
- Expected decrease in lymphocytes

Evolving Definitions of Remission in UC

Clinical Remission



Mayo score 0-1 with
no bleeding

PRO

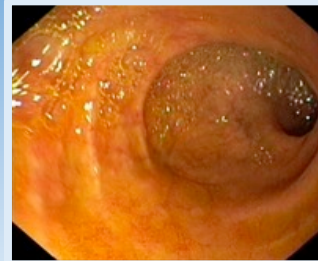
Diarrhea 0
Bleeding 0

Biologic Remission



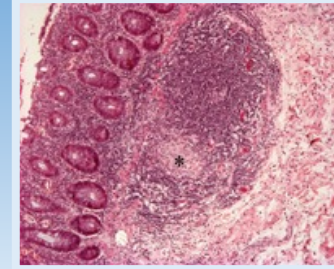
PRO 0+
Endoscopy 0-1

Endoscopic Remission



Mayo endoscopy
subscore of 0
(normal) or 1

Histologic Remission



Various indices

Robarts
Geboes

PRO, patient-reported outcomes.

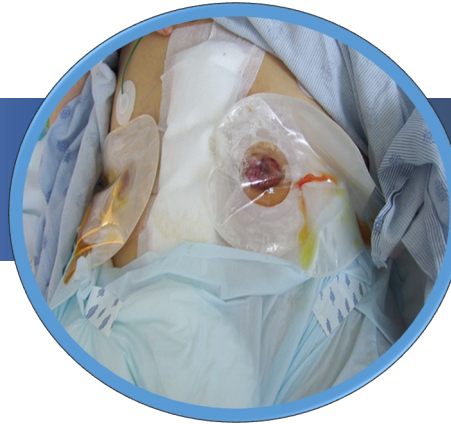
1. Rogler G et al. *World J Gastroenterol*. 2013;19(43):7552-7560. 2. Walsh AJ et al. *Nature Rev Gastroenterol Hepatol*. 2016;13:567-579.

Treatment Strategies for UC Are Driven By Patient Risk of Complicated Disease

5-ASAs & limited steroids

Low risk (~40%)
for colectomy

Limited anatomic extent
Mild endoscopic disease



Early advanced therapies

High risk (~60%)
for colectomy

Age <40 years
Extensive colitis
Deep ulcers
Corticosteroid dependent
History of hospitalization
High CRP and ESR
C difficile infection
CMV infection

adopted from Dassopoulos T, Scherl, E, Schwartz R, Kosinski L, Cohen C, and Regueiro M
Gastroenterology. 2015;149:238-245.

Which therapy first, second, third..... for UC?

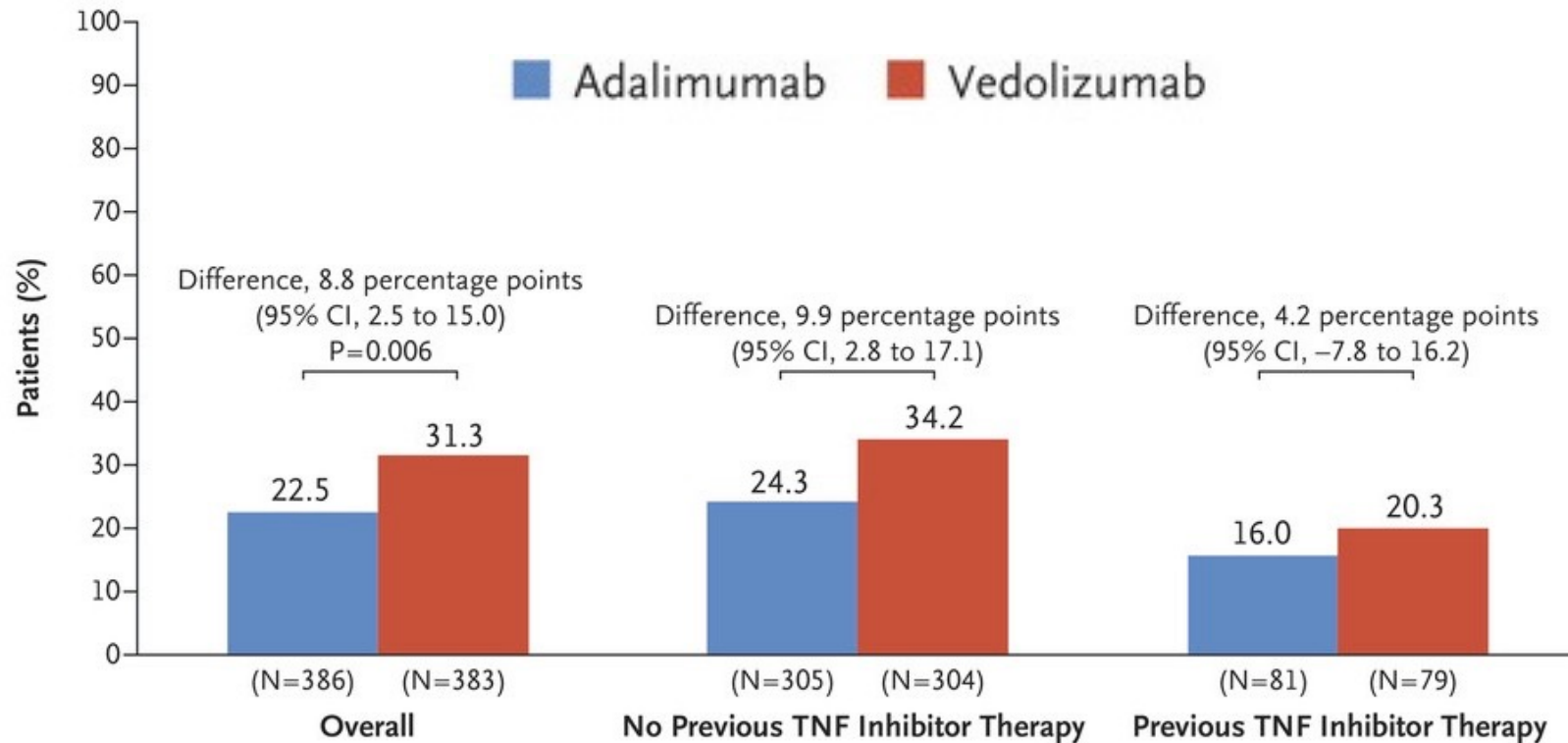
Only One Head to Head published UC study

We Rely on Network Meta-analysis, not perfect, but
that's the best we have at this time

Randomized, Controlled Trial of Vedolizumab vs Adalimumab in Patients with Active UC (VARSITY)

N=769, VDZ (n=383) or ADA (n=386)

Clinical Remission and Mucosal Healing at Week 52



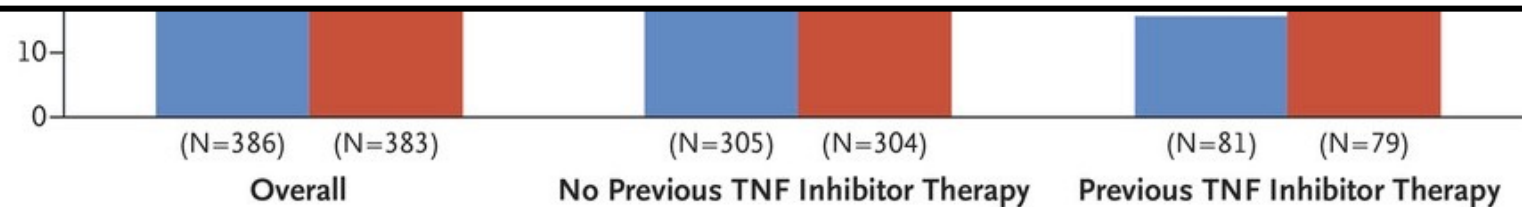
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Clinical Remission and Mucosal Healing at Week 52

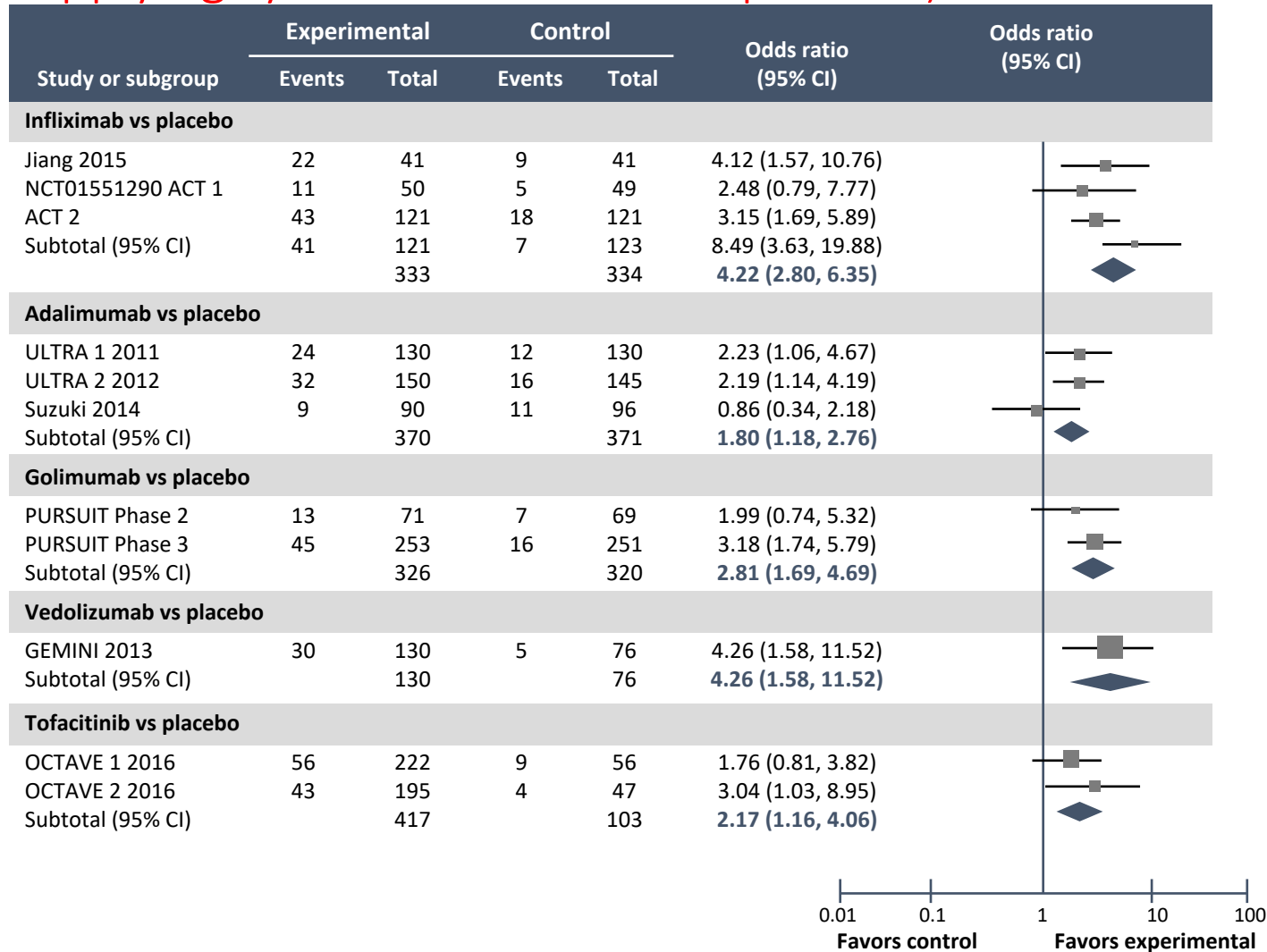
Limitations to VARSITY:

- No dose escalation
- No drug levels
- If on steroids or IMMs, no difference between groups



Systematic Review with Network Meta-Analysis (2018):

First-Line Induction Pharmacotherapy for Moderate to Severe Ulcerative Colitis
(caution applying systematic reviews to practice)

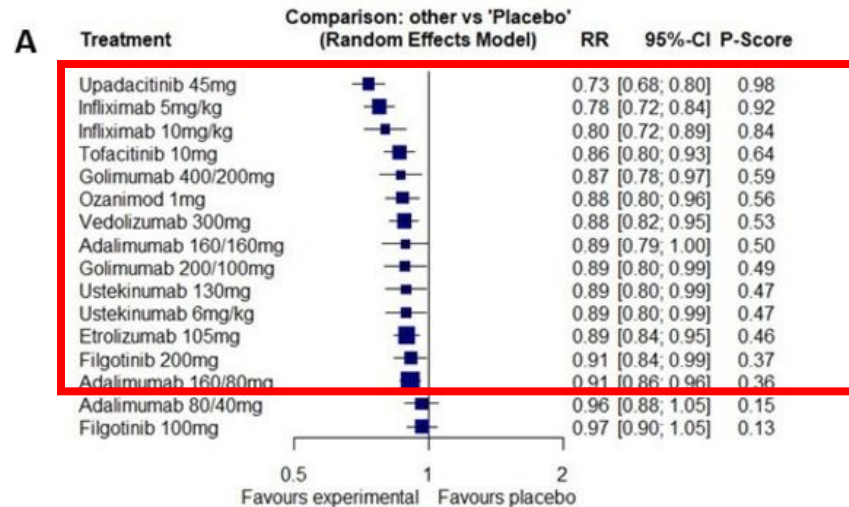


Effect size was positive
for all treatments
(compared to control)

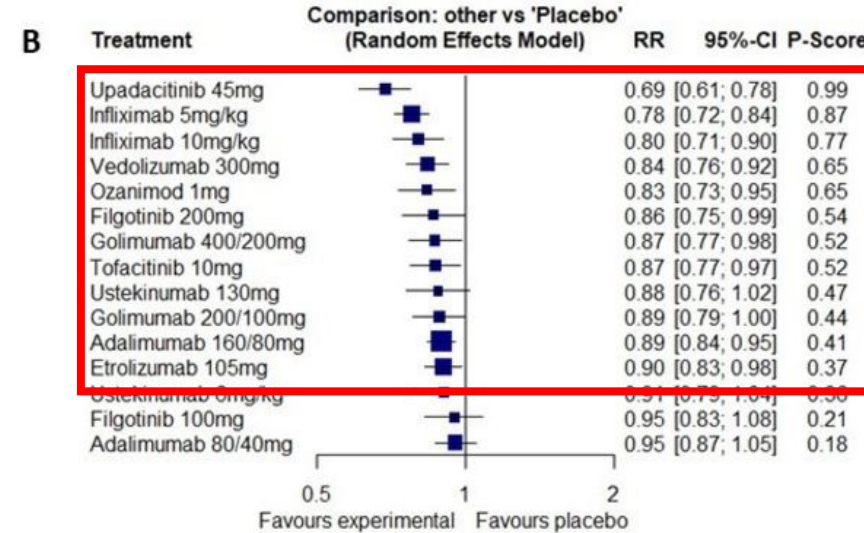
Strongest
for vedolizumab
and infliximab

Positioning Therapies for Moderate to Severe UC: Clinical Remission (2021)

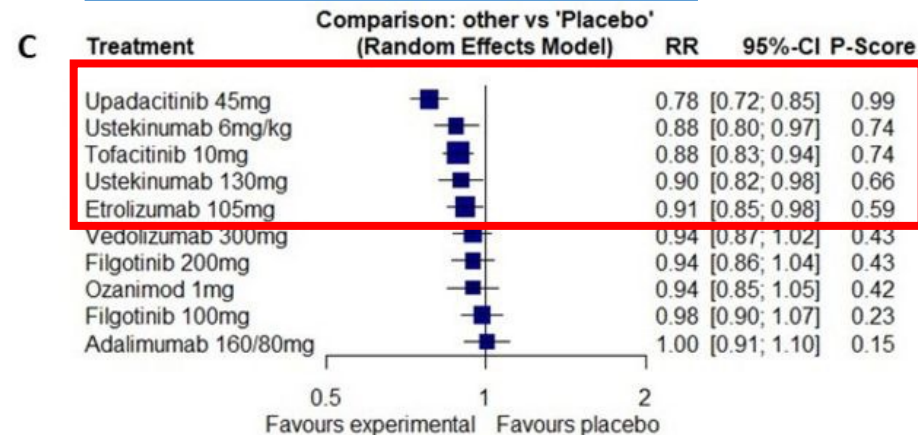
All Patients (+++ UPA, IFX. + TOFA, OZA, GOL, VEDO, ADA)



Anti-TNF Naïve (++ UPA, IFX. + VEDO, OZA, FIL, GOL, TOFA)



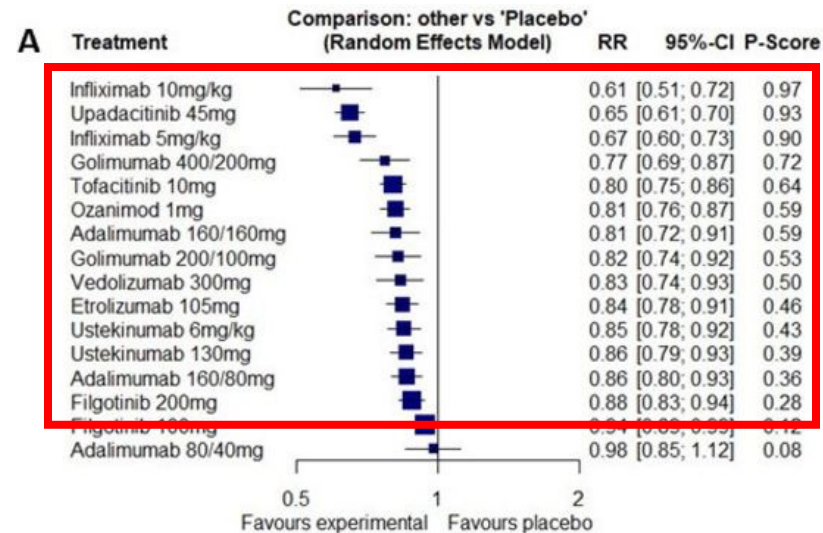
Anti-TNF Exposed (++ UPA. + UST, TOFA)



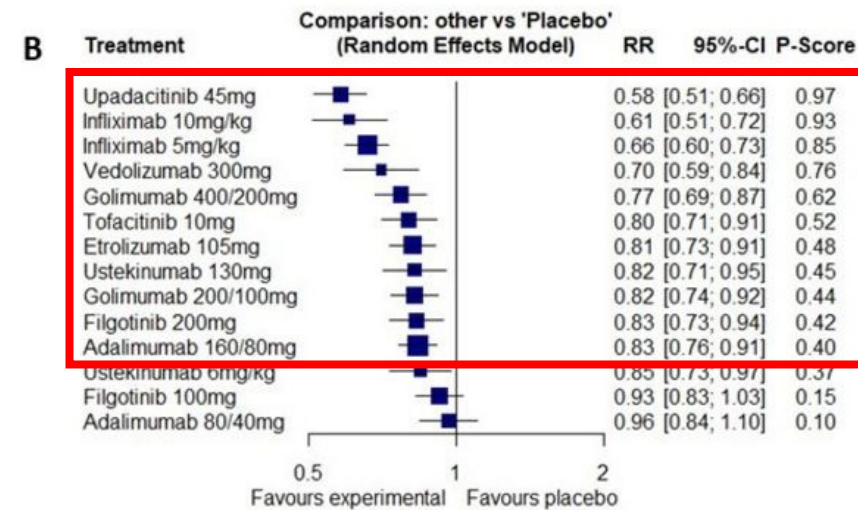
- 28 trials, 12504 patients
- Endpoints Wk 6-14
- UPA & IFX 1st for Efficacy

Positioning Therapies for Moderate to Severe UC: Endoscopic Improvement (2021)

All Patients (+++ UPA, IFX. + GOL, TOFA, OZA, ADA, VEDO, UST, FIL)

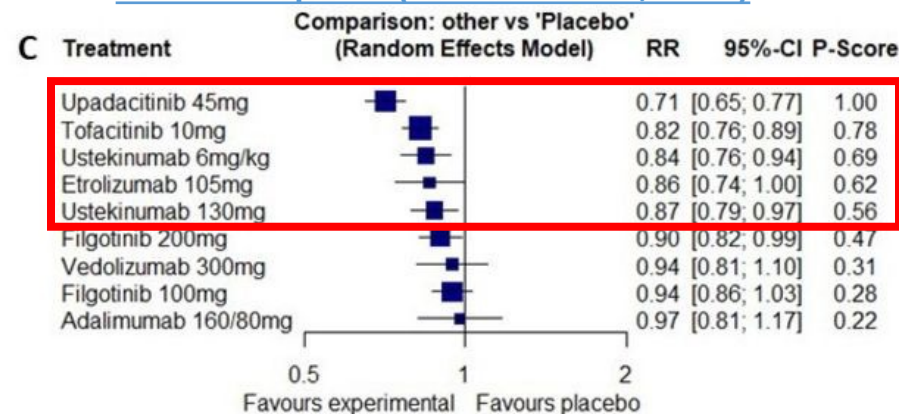


Anti-TNF Naïve (+++ UPA, IFX. + VEDO, GOL, TOFA, FIL, ADA)



- 27 trials, 11733 patients
- Endpoints Wk 6-14
- IFX & UPA 1st for Efficacy overall
- Upadacitinib 45 mg superior to all drugs in anti-TNF exposed
- Ozanimod not evaluated in sub-groups for endoscopic data

Anti-TNF Exposed (+++ UPA. + UST, TOFA)



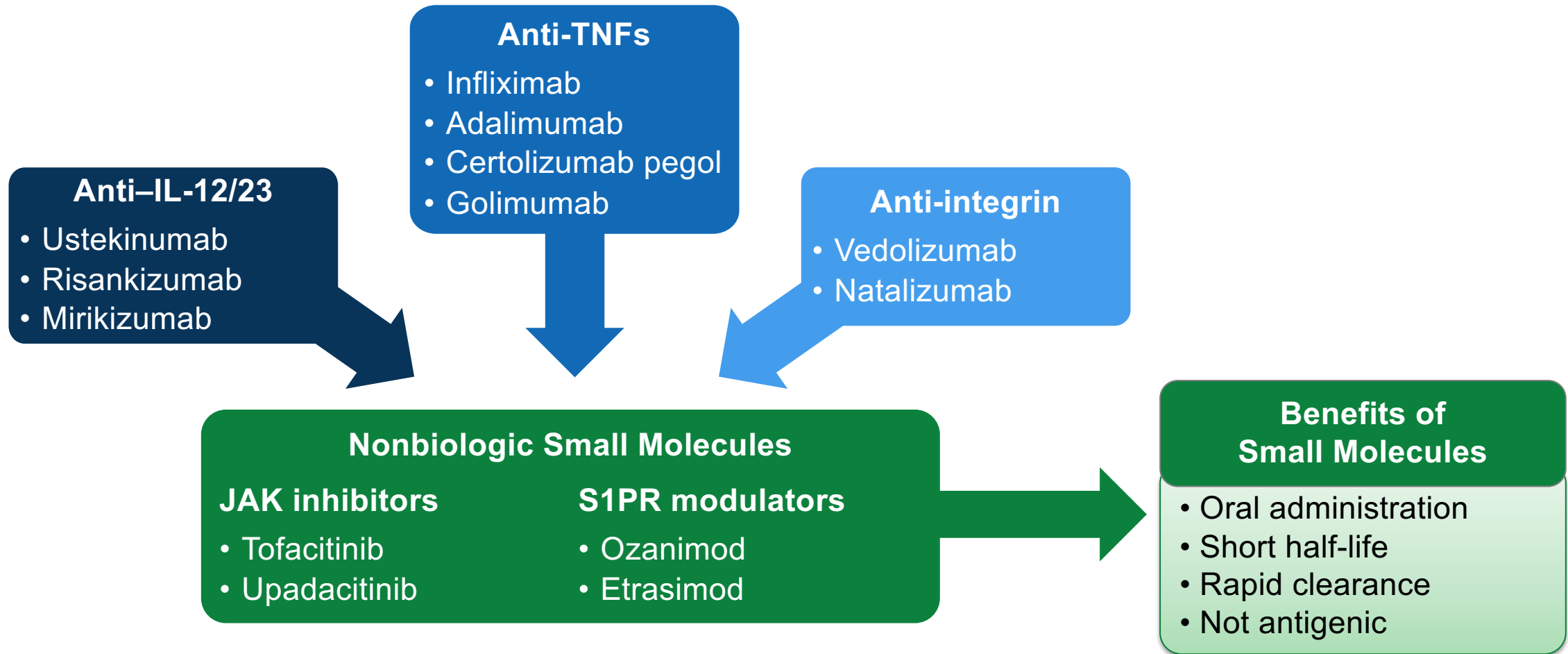
Adverse Events:

- No drug more likely than placebo to lead to SAE
- RR of SAE significantly less with Vedo and Golimumab than placebo
- Upa 45 mg most likely to lead to AE and Ust 130 mg least likely
- Tofa 10 mg bid ranked last for infections (significant compared to placebo)

Network Meta-analysis Ulcerative Colitis

Upadacitinib	2.70 (1.18-6.20)	4.49 (2.18-9.24)	6.15 (2.98-12.72)	2.84 (1.28-6.31)	4.91 (2.59-9.31)	2.92 (1.31-6.51)	3.56 (1.84-6.91)	3.00 (1.32-6.82)	4.64 (2.47-8.71)	2.70 (1.18-6.20)	9.54 (5.45-16.69)	Clinical remission
3.01 (1.59-5.67)	Ozanimod	1.65 (0.77-3.55)	2.27 (1.05-4.89)	1.05 (0.45-2.41)	1.81 (0.91-3.60)	1.07 (0.46-2.49)	1.31 (0.65-2.67)	1.10 (0.47-2.61)	1.71 (0.87-3.37)	0.93 (0.47-1.85)	3.52 (1.91-6.49)	
2.91 (1.19-7.10)	0.97 (0.39-2.39)	Filgotinib 200 mg	1.37 (0.71-2.62)	0.63 (0.30-1.31)	1.09 (0.63-1.89)	0.65 (0.31-1.35)	0.79 (0.44-1.41)	0.66 (0.31-1.42)	1.03 (0.60-1.77)	0.56 (0.32-0.97)	2.12 (1.34-3.35)	
5.96 (2.35-15.14)	1.98 (0.77-5.09)	2.04 (0.66-6.33)	Filgotinib 100 mg	0.46 (0.22-0.95)	0.79 (0.45-1.39)	0.47 (0.22-0.99)	0.57 (0.32-1.03)	0.48 (0.22-1.03)	0.75 (0.43-1.30)	0.41 (0.23-0.71)	1.54 (0.97-2.45)	
3.05 (1.68-5.51)	1.01 (0.55-1.86)	1.04 (0.43-2.50)	0.51 (0.20-1.27)	Tofacitinib	1.72 (0.90-3.29)	1.02 (0.45-2.30)	1.25 (0.64-2.45)	1.05 (0.46-2.41)	1.63 (0.86-3.08)	0.89 (0.46-1.69)	3.35 (1.90-5.91)	
4.71 (2.83-7.83)	1.56 (0.92-2.66)	1.61 (0.71-3.65)	0.78 (0.33-1.86)	1.54 (0.96-2.48)	Etrolizumab	0.59 (0.31-1.14)	0.72 (0.48-1.08)	0.61 (0.31-1.21)	0.94 (0.69-1.29)	0.51 (0.36-0.72)	1.94 (1.42-2.64)	
3.45 (1.90-6.24)	1.14 (0.62-2.11)	1.18 (0.49-2.83)	0.57 (0.23-1.44)	1.13 (0.64-1.99)	0.73 (0.45-1.18)	Ustekinumab	1.22 (0.62-2.39)	1.02 (0.44-2.35)	1.59 (0.83-3.02)	0.86 (0.45-1.66)	3.26 (1.83-5.79)	
4.71 (2.68-8.28)	1.56 (0.87-2.81)	1.61 (0.68-3.79)	0.79 (0.32-1.93)	1.54 (0.90-2.63)	1.00 (0.64-1.55)	1.36 (0.79-2.33)	Vedolizumab	0.84 (0.41-1.68)	1.30 (0.96-1.74)	0.71 (0.45-1.10)	2.67 (1.87-3.80)	
4.52 (2.55-8.01)	1.50 (0.83-2.72)	1.54 (0.65-3.65)	0.75 (0.30-1.86)	1.48 (0.86-2.55)	0.95 (0.61-1.51)	1.31 (0.76-2.26)	0.95 (0.57-1.60)	Golimumab	1.54 (0.79-3.01)	0.84 (0.43-1.65)	3.17 (1.74-5.79)	
5.41 (3.30-8.86)	1.79 (1.07-3.01)	1.85 (0.82-4.15)	0.90 (0.38-2.12)	1.77 (1.11-2.81)	1.14 (0.88-1.49)	1.56 (0.98-2.48)	1.15 (0.75-1.75)	1.19 (0.77-1.84)	Adalimumab	0.54 (0.37-0.79)	2.05 (1.54-2.73)	
2.75 (1.66-4.55)	0.91 (0.54-1.54)	0.94 (0.41-2.14)	0.46 (0.19-1.09)	0.90 (0.56-1.44)	0.58 (0.43-0.78)	0.79 (0.49-1.27)	0.58 (0.37-0.91)	0.60 (0.39-0.95)	0.51 (0.37-0.69)	Infliximab	3.76 (2.77-5.12)	
8.23 (5.32-12.75)	2.74 (1.72-4.34)	2.82 (1.30-6.12)	1.38 (0.60-3.14)	2.71 (1.81-4.02)	1.74 (1.34-2.26)	1.74 (1.34-2.26)	1.74 (1.22-2.49)	1.82 (1.25-2.63)	1.52 (1.21-1.92)	3.00 (2.33-3.82)	Placebo	
Endoscopic improvement												

Evolution of Therapeutic Targets for IBD: Monoclonal Antibodies and Small Molecules¹⁻³



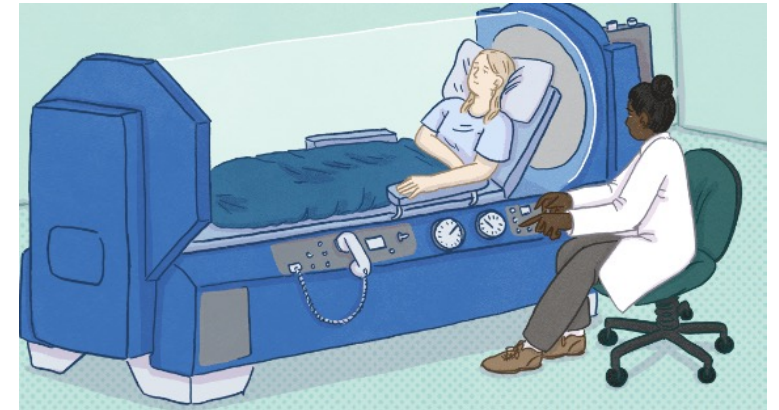
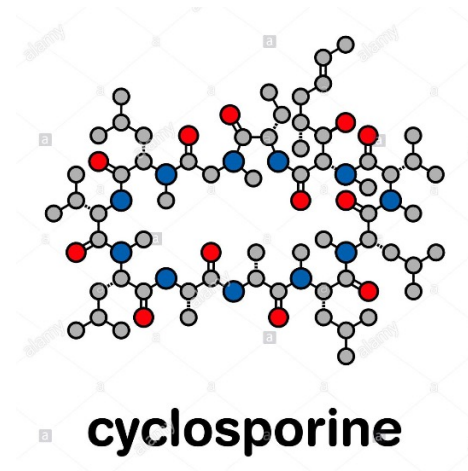
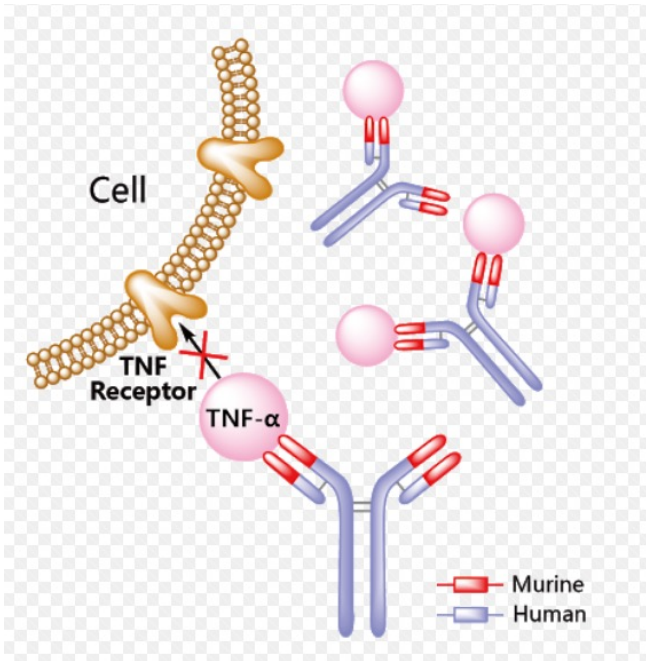
Acute Severe Ulcerative Colitis (ASUC)

Positioning Therapies

Therapy Choices when Failing IV Corticosteroids

What therapy is best in patients with severe UC that is refractory to steroids?

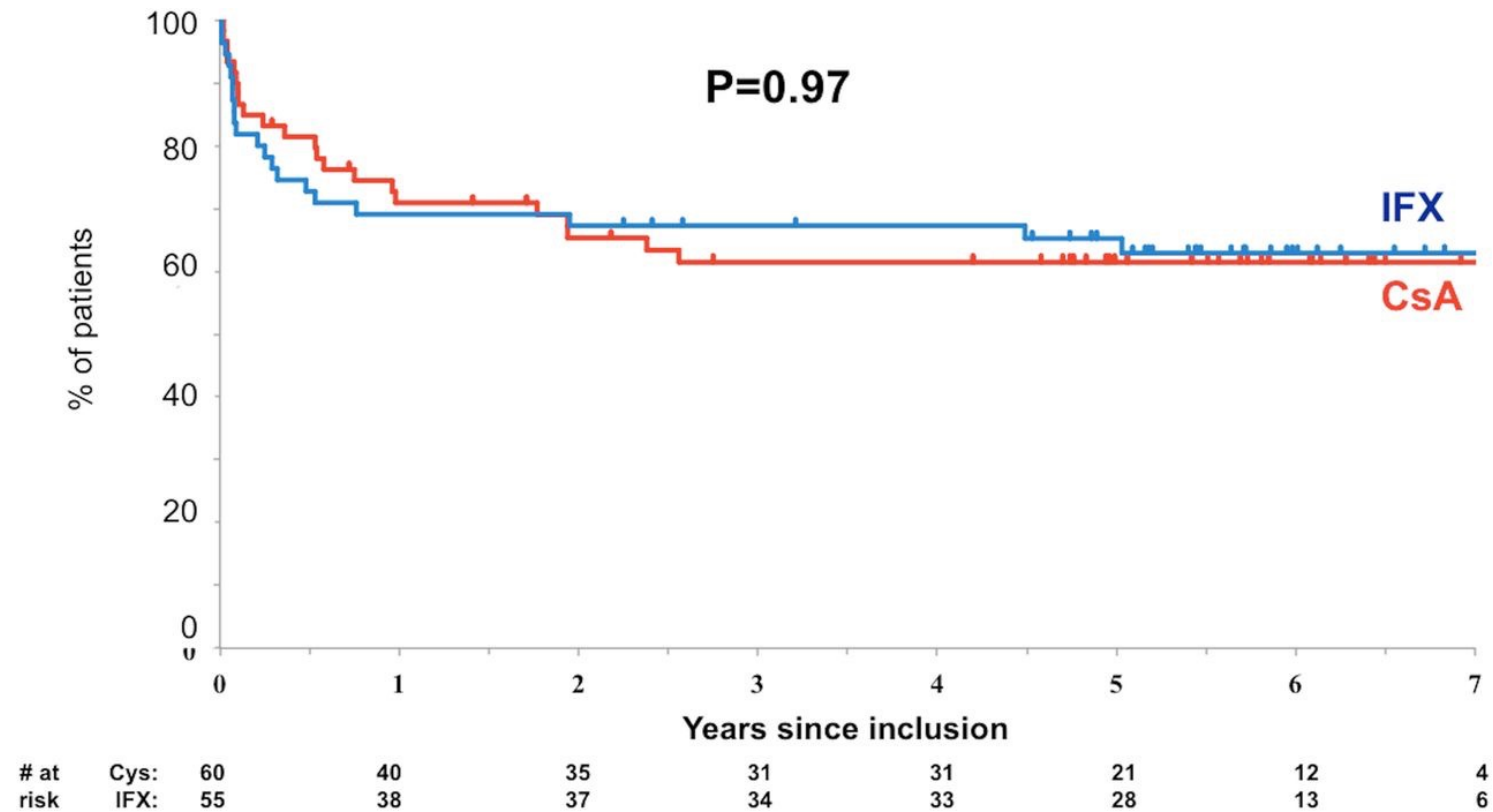
- Infliximab
- Cyclosporine
- Tofacitinib 10mg TID?
- Hyperbaric oxygen?



Medical Options for the High-Risk UC Inpatient

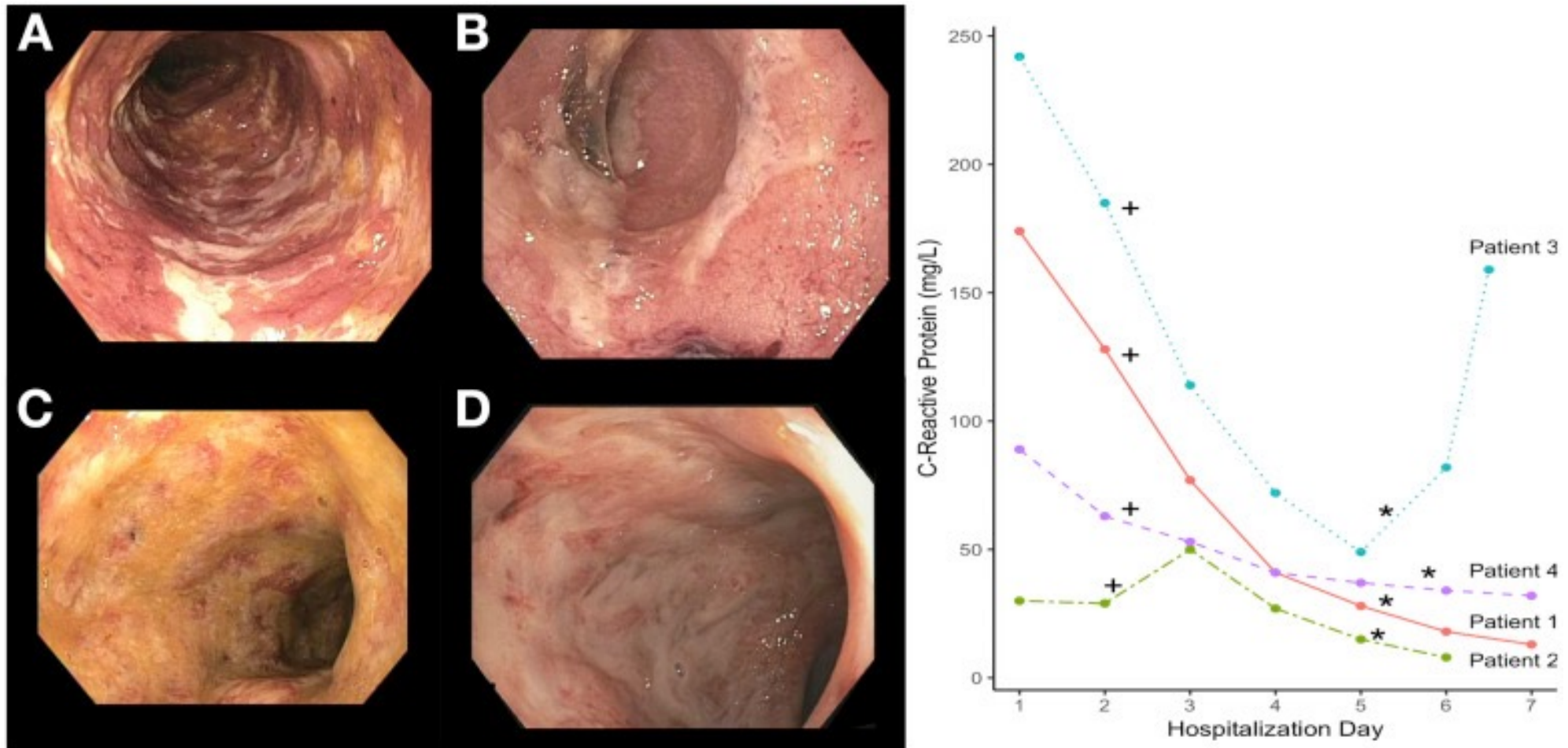
Treatment	Induction	Dose	Duration of Induction Dosing	Maintenance	Maintenance Options
Steroids (IV)	✓	Medrol 60 mg qd Hydrocortisone 100 mg TID/QID	3-7 days	X	• Thiopurine • Anti-TNF ± thiopurine or MTX • Vedolizumab • Ustekinumab • Tofacitinib (if failed anti-TNF)
Infliximab	✓	5 or 10 mg/kg IV	0, 2, 6 w Possible accelerated dosing	✓	Unknown if dose reduction possible after accelerated dosing for induction
Cyclosporine (IV)	✓	2-4 mg/kg IV continuous Target 300-400	7-14 days	X	• Thiopurine • Vedolizumab • Ustekinumab • Ozanimod
Tofacitinib (maybe upadacitinib)	✓	10mg TID (UPA 30mg bid?)	?		

Infliximab or Cyclosporine are Effective for ASUC: Long Term Comparison of Colectomy Free Survival is also no different



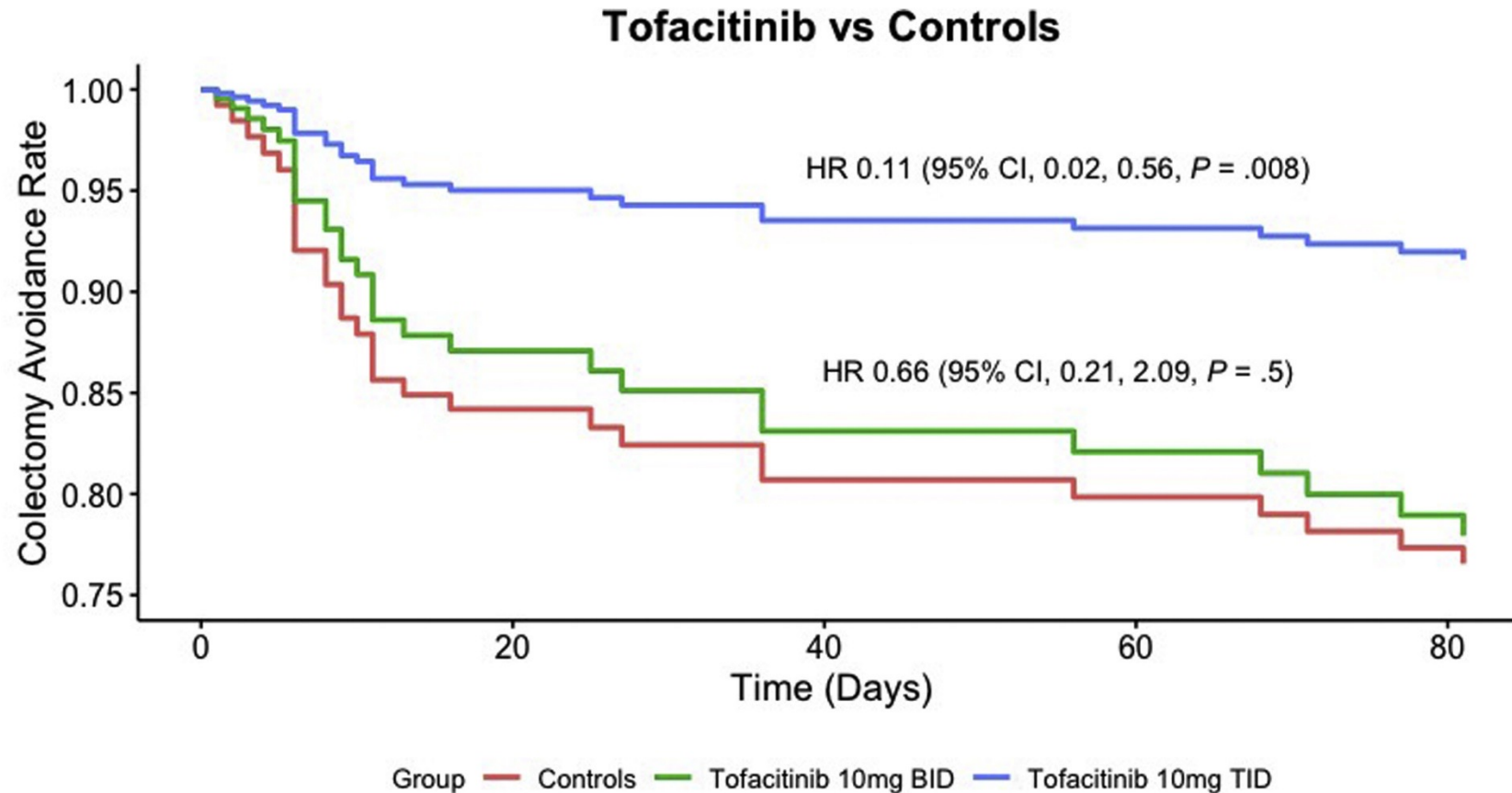
Kaplan-Meier curves of colectomy-free survival according to treatment given at inclusion.

Tofacitinib for Acute Severe Ulcerative Colitis

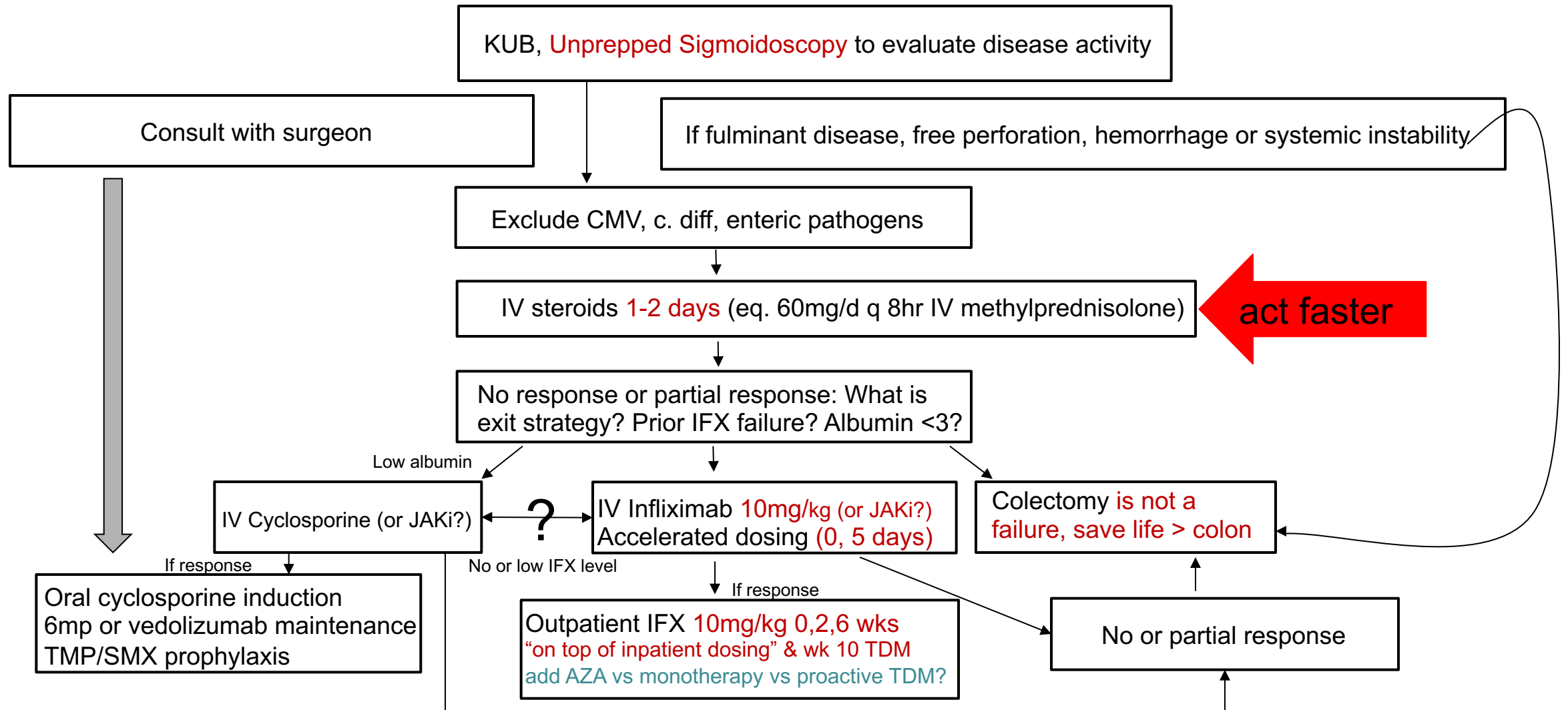


Berinstein JA, et al. Clin Gastroenterol Hepatol 2019;17:988–990.
Kotwani P, et al. J Crohns Colitis. 2020; 14: 1026–1028

Tofacitinib 10 mg TID (vs BID and placebo) and Avoidance of Colectomy



Algorithm for the Management of ASUC (Miguel's practice)

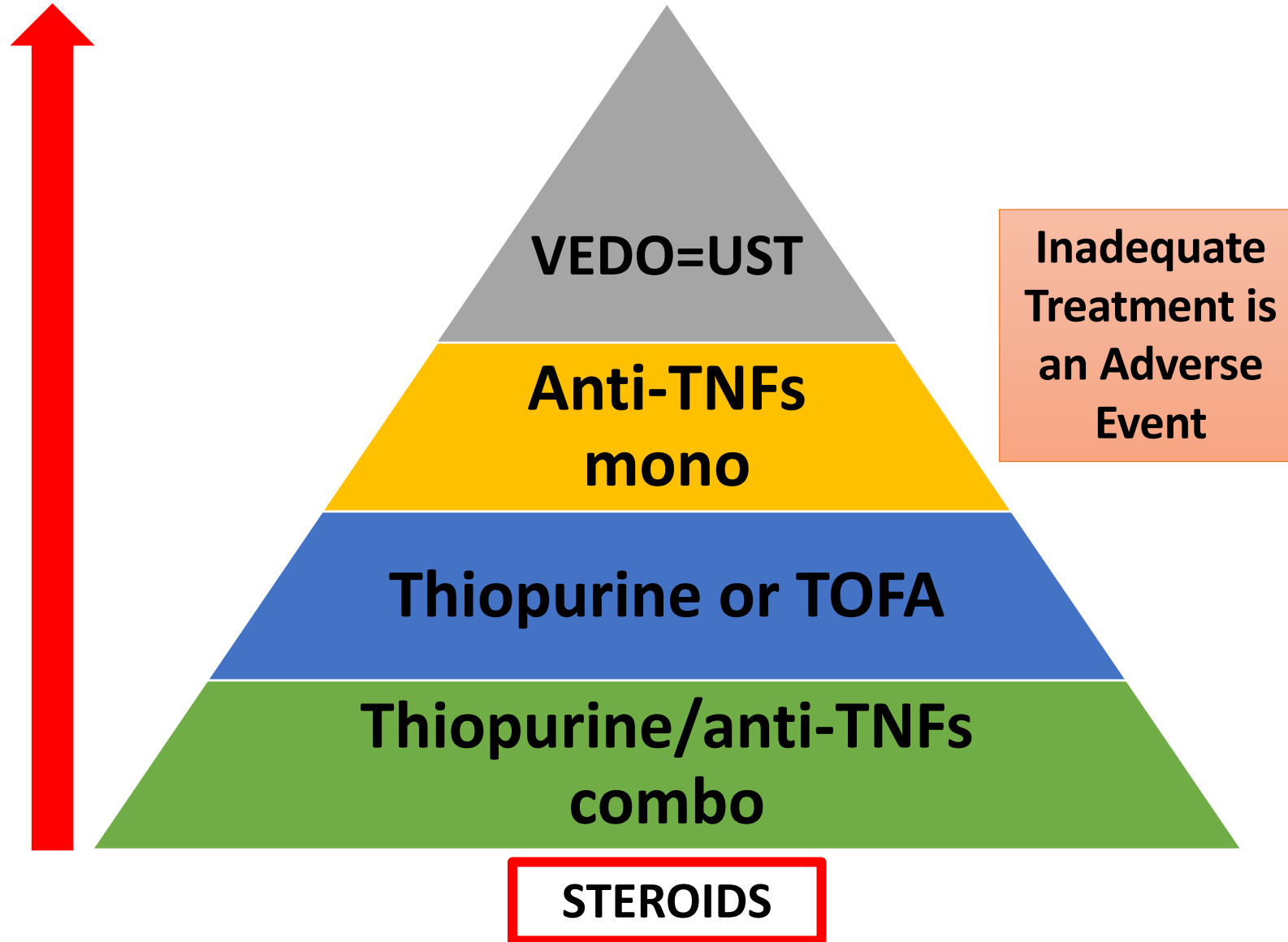


The Evolution of the Safety Pyramid

Safety considerations for positioning therapies

The Modified Safety pyramid of current IBD meds

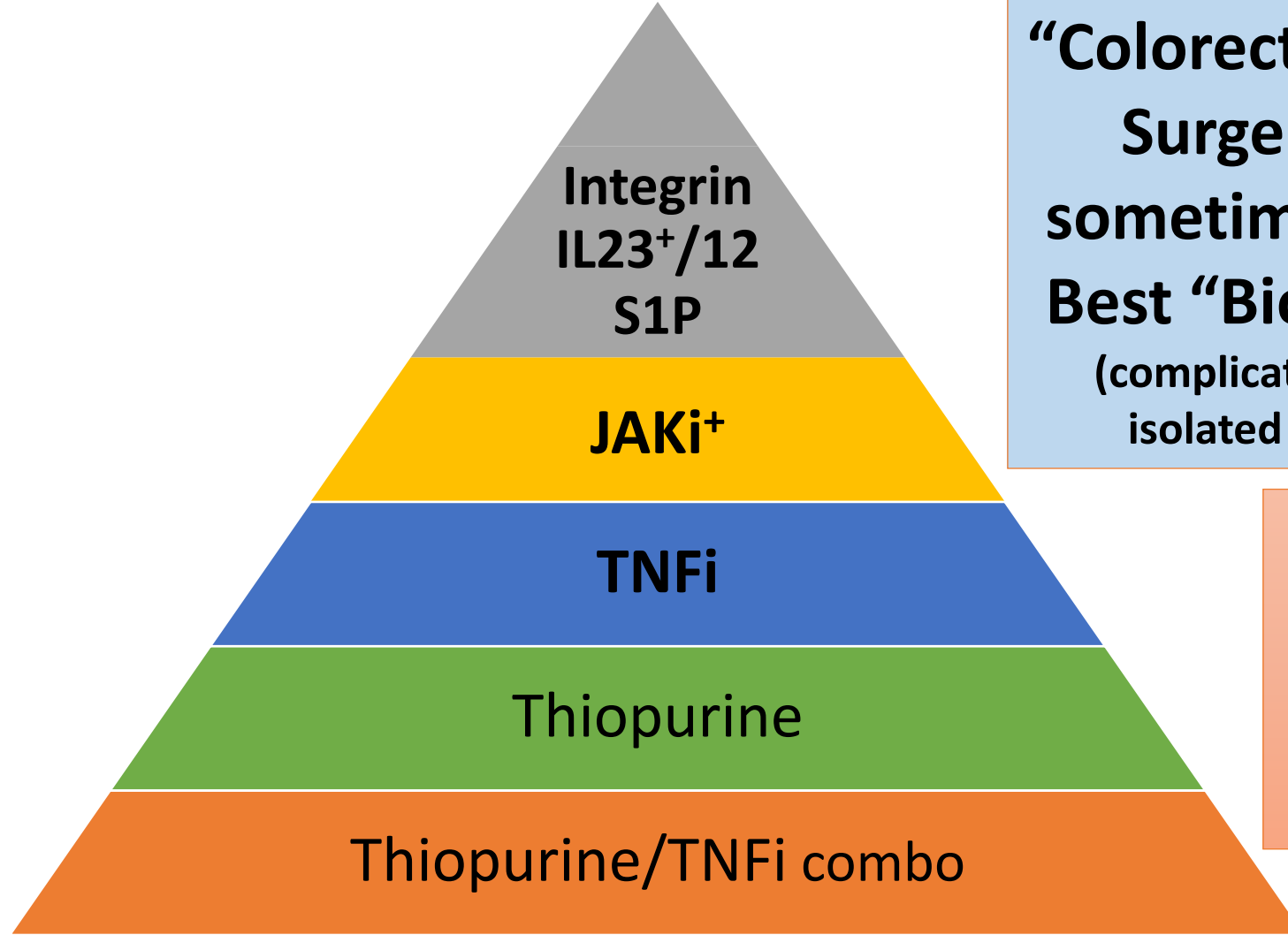
Safest *(Queiroz, Regueiro Curr Opinion Gastro 2019)*



*The Safety Pyramid of Today **

(Bhat, Click, Regueiro IBDj 2023)

Safest



“Colorectomab”
Surgery is
sometimes the
Best “Biologic”
(complications or
isolated TI ds)

**Inadequate
Treatment is
an Adverse
Event**

⁺Does selectivity = safer?

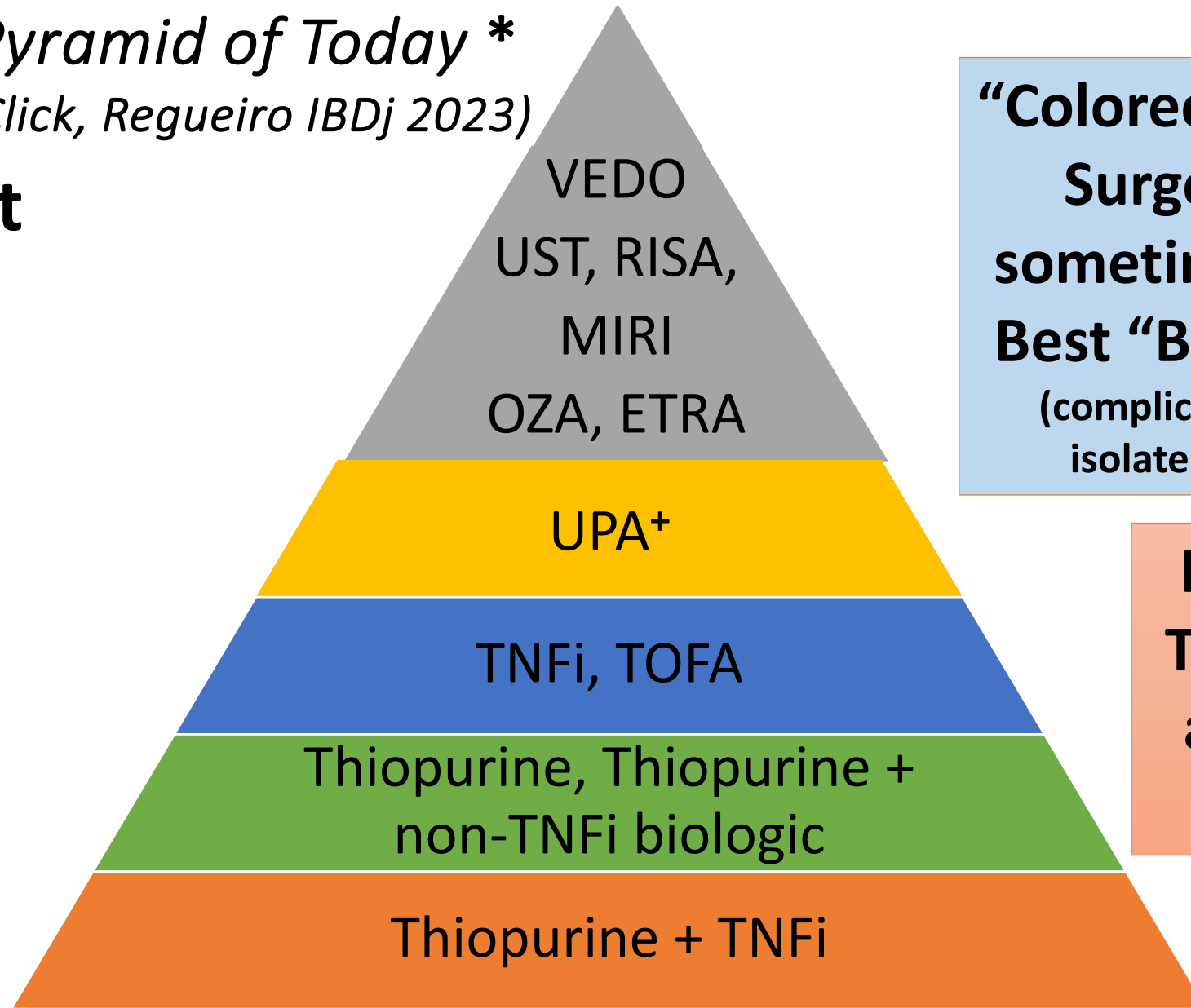
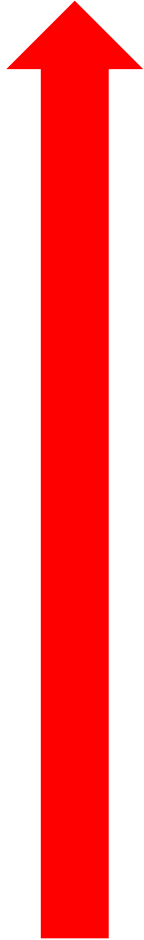
STERIODS

*These are my opinions, not
based on head-to-head data

*The Safety Pyramid of Today **

(adapted Bhat, Click, Regueiro IBDj 2023)

Safest



“Colorectomab”
Surgery is
sometimes the
Best “Biologic”
(complications or
isolated TI ds)

**Inadequate
Treatment is
an Adverse
Event**

⁺Does selectivity = safer?

STERIODS

*These are my opinions, not
based on head to head data

Biologics & Small Molecules for IBD “Which One Today?” – Miguel’s Practice

many insurances require TNFi (biosimilar) first (FDA note: JAKi only after TNFi)

- **UC severe** (hospitalized or “pending” hospitalization or “severe end of moderate”)
 - 1st IFX (up to 10mg/kg) with AZA (MTX young males), 2nd UPA>TOFA (more data needed for inpatients)
- **UC: outpatient moderate** (not “impending” hospitalization)
 - 1st VEDO or UST or MIRI or OZA or ETRA or TNFi, 2nd UPA>TOFA (if TNFi was 1st)
The milder end of moderate UC pts failing 5-ASA may be the S1P “sweet spot” – don’t linger on steroids!
- **Extraintestinal manifestations**
 - Secondary to bowel inflammation (peripheral arthritis, EN): any med that heals bowel inflammation
 - Pyoderma gangrenosum, Uveitis, Central Arthritis: TNFi/MTX (UST or RISA or MIRI - skin, TOFA or UPA - joints)
- **Pregnancy** – any monoclonal Ab is ok throughout pregnancy: **stop** MTX > 3 mos and stop OZA, ETRA, TOFA or UPA > 1 mos prior to conception

Thank you!

