Διαφοροποίηση της δράσης των φαρμάκων σε παθήσεις με κοινούς παθογενετικούς μηχανισμούς: το παράδειγμα των ΙΦΝΕ

Ιωάννης Δρυγιαννάκης, MD PhD FEBGH

Γαστρεντερολόγος – Γαστρεντερολογική κλινική, Πανεπιστημιακό Νοσοκομείο Ηρακλείου

Πανεπιστημιακός Υπότροφος – Ερευνητικό Εργαστήριο Γαστρεντερολογίας, Ιατρική Σχολή, Πανεπιστήμιο Κρήτης

Ηράκλειο, 29 Σεπτεμβρίου 2023

Δήλωση σύγκρουσης συμφερόντων

- Pfizer Inc. − Competitive grant # 64132481 under the call “Inflammation ASPIRE 2020 Ulcerative colitis”

- Pfizer Inc. − 2022 Inflammatory Bowel Disease Fellowship Grant # 75391309

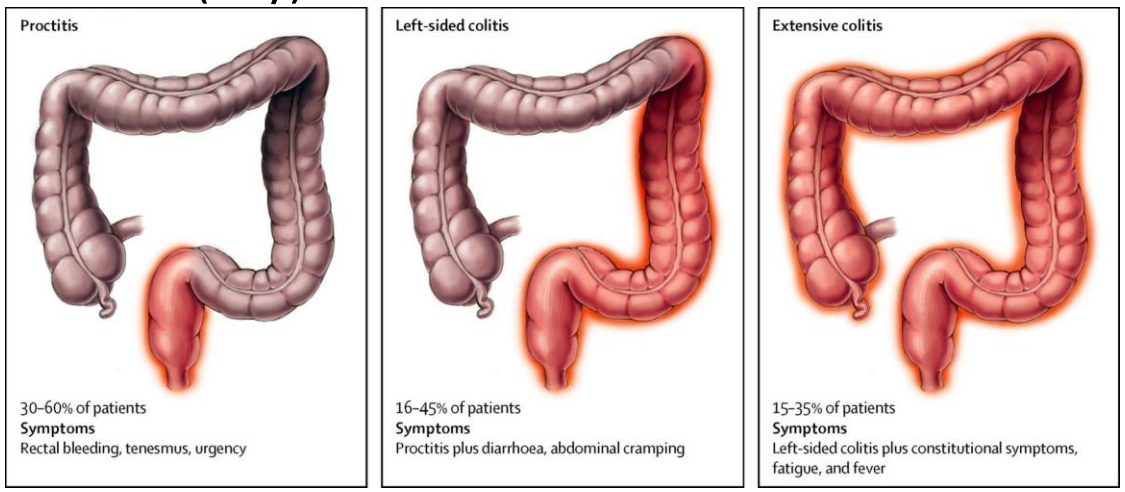
IBD by Montreal classification

CD

Age at diagnosis	A1 below 16 y A2 between 17 and 40 y A3 above 40 y
Location	L1 ileal L2 colonic L3 ileocolonic L4 isolated upper disease*
Behaviour	B1 non-stricturing, non-penetrating B2 stricturing B3 penetrating p perianal disease modifier†

UC

E1 50% (10y)→ E2 E3



Factors not taken into account…

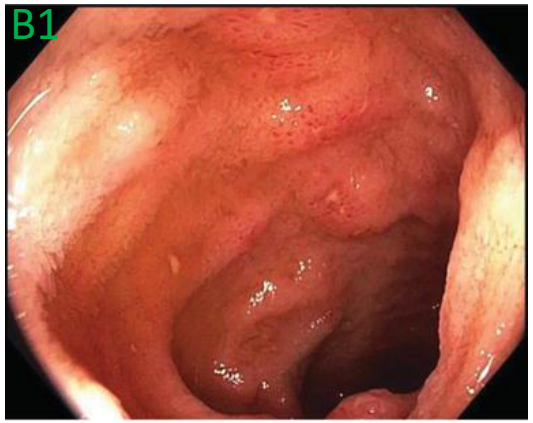
- medication needs
- surgeries
- frequency of exacerbations
- other aggravating factors

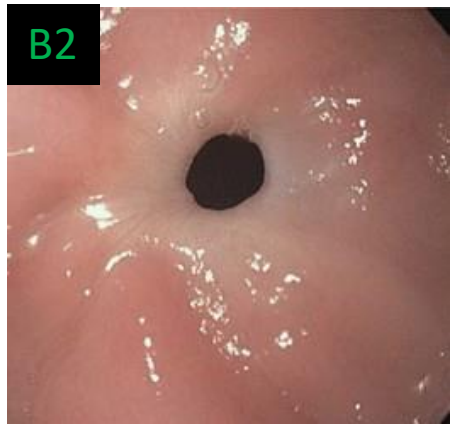
- B2: inflammatory or fibrotic ?
- B3 as a mechanistic result of B2 or not?

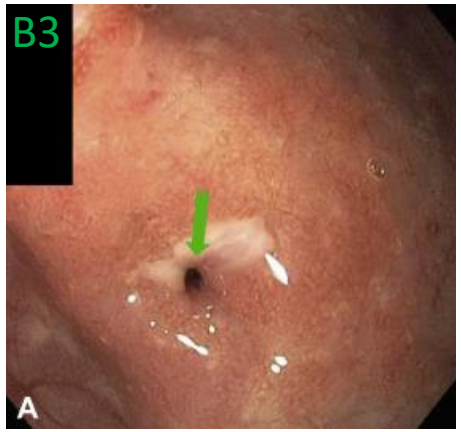
UC: ulcerative colitis, CD: Crohn's disease

Satsangi J et al. Gut 2006;55(6):749-53.

Diagnosis





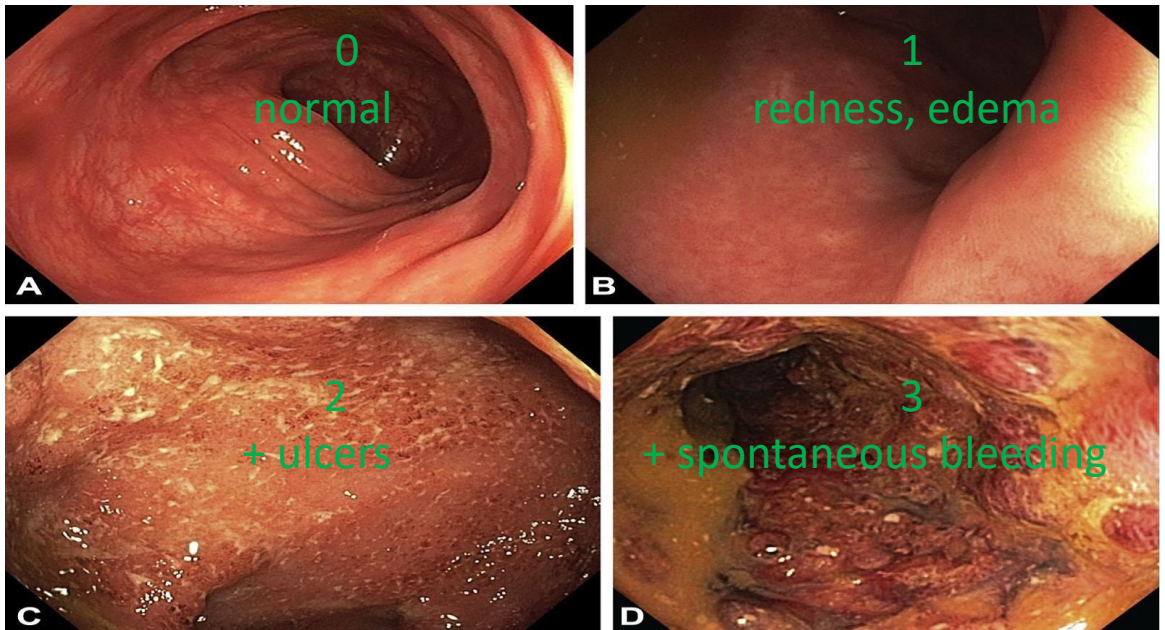


- Symptoms
  - ✓ >3 bowel movements/24h ≥4-6w
  - ✓ upper GI
  - ✓ occlusive
  - ✓ low-grade fever
- Biomarkers of inflammation
  - ✓ ↑ CRP
  - ✓ ↑ ESR
  - ✓ ↑ PLT
  - ✓ ↓ Hb
  - ✓ ↓ Alb
- Endoscopy (*the gold-standard*)

  <u>Crohn's disease</u>
  - Aphthous ulcers within normal mucosa
  - Stenosis
  - Fistula

  <u>Ulcerative colitis</u>

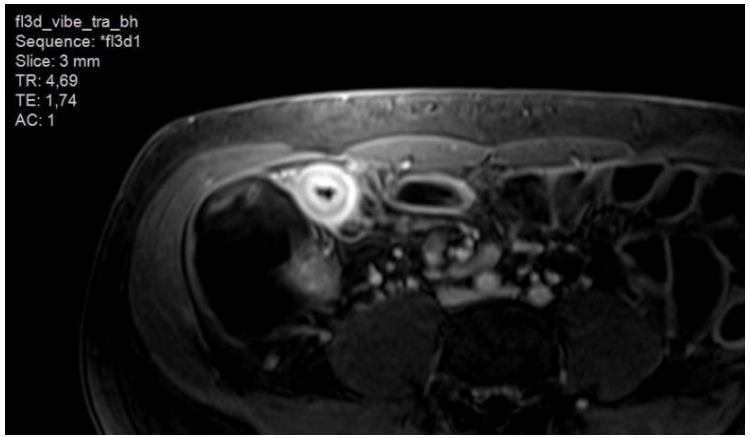
Endoscopic Mayo score



Magnetic resonance enterography (MRE) - Histology

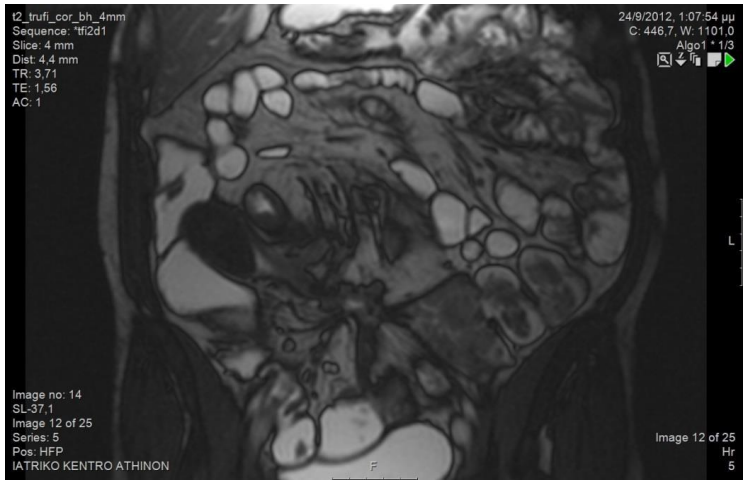
Wall

- thickening
- layering
- ulcers



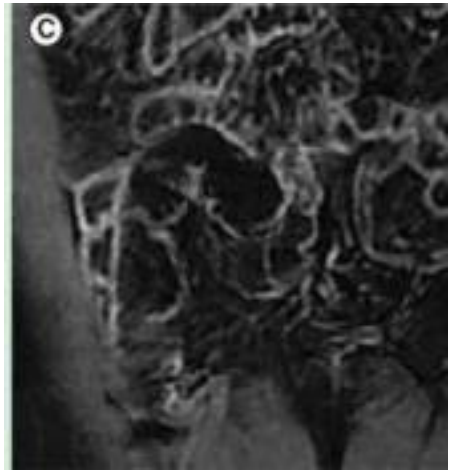
Fistulae

- Star sign

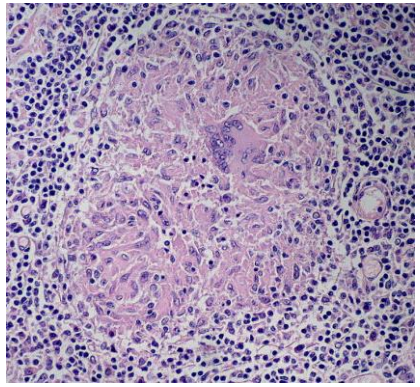


Lumen

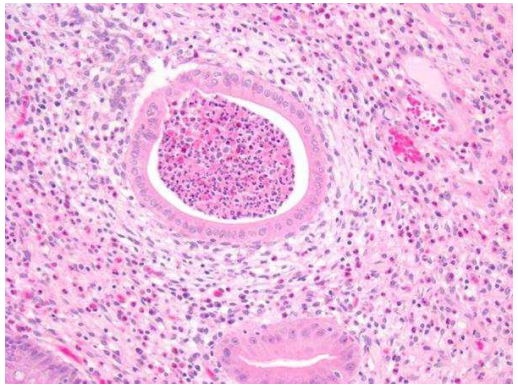
- stenoses
- pre-stenotic dilatation



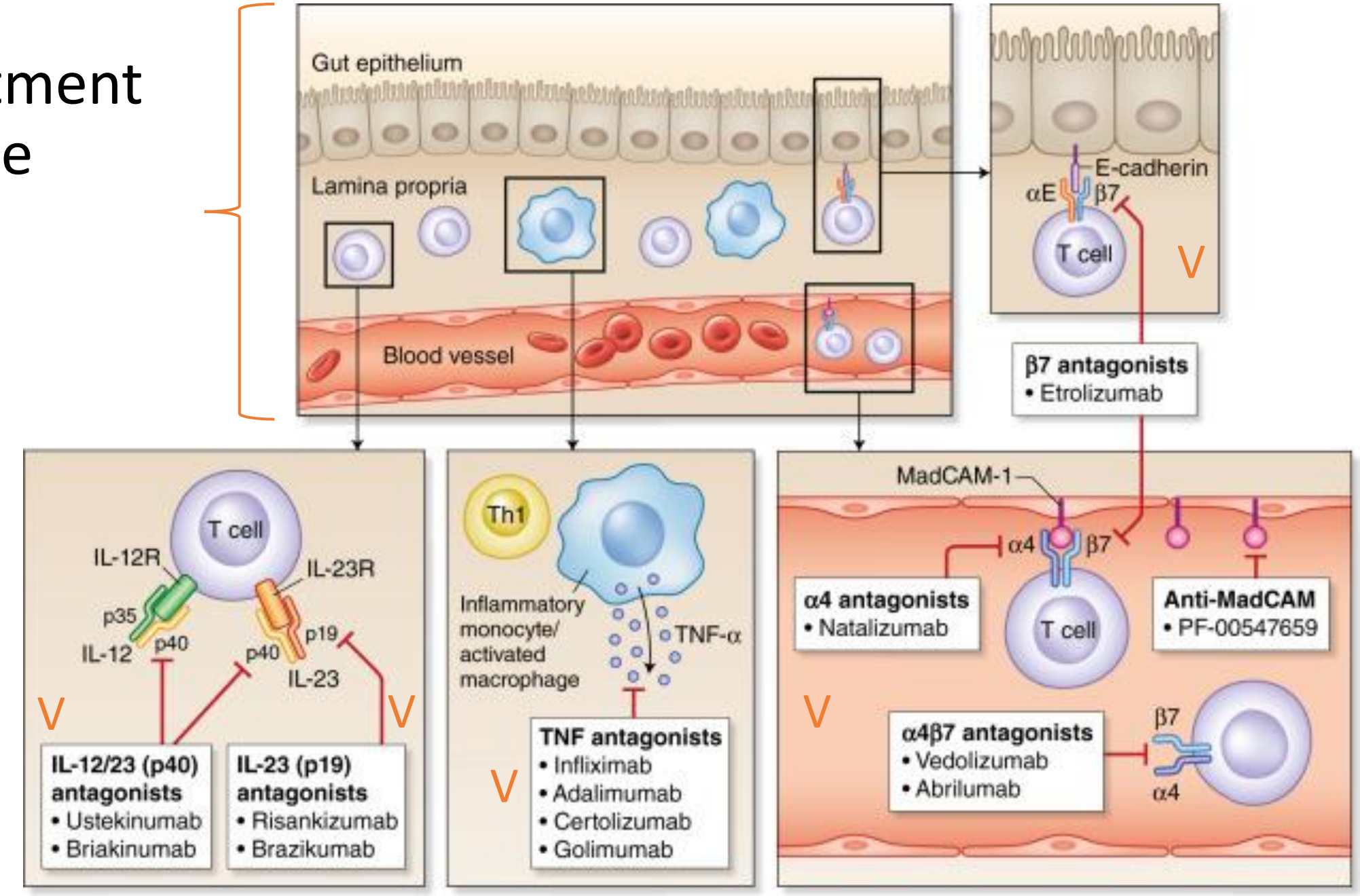
Non-caseating granuloma



Cryptic abscess



IBD treatment landscape

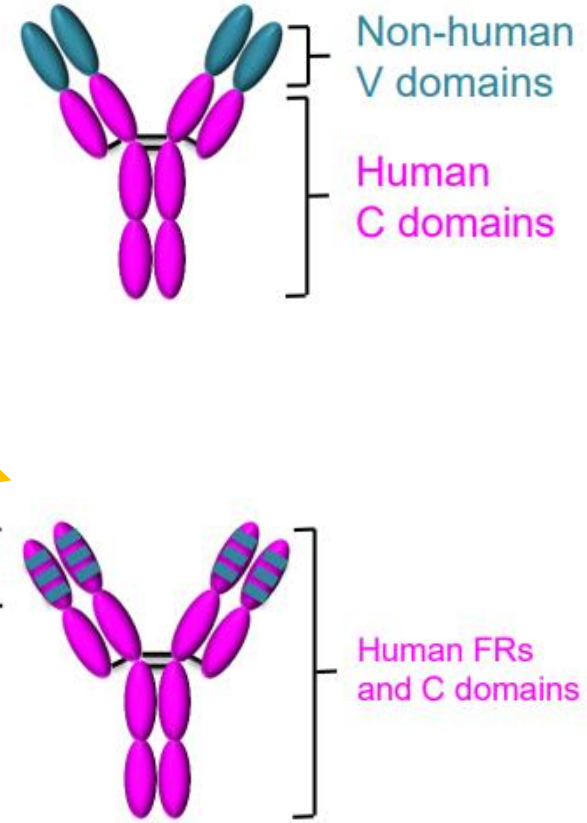


Paramsothy S et al. Mucosal Immunol 2018;11(6):1558-70.

Biologics: antibodies

Common Antibody Origin		INN Substem	Representative Examples
Chimeric	<85%	-xi-	Abciximab, Rituximab, Infliximab, Cetuximab
Humanized	>85%	-zu-	Palivizumab, Trastuzumab, Bevacizumab, Natalizumab
Human		-u-	Adalimumab, Panitumumab Golimumab, Ipilimumab

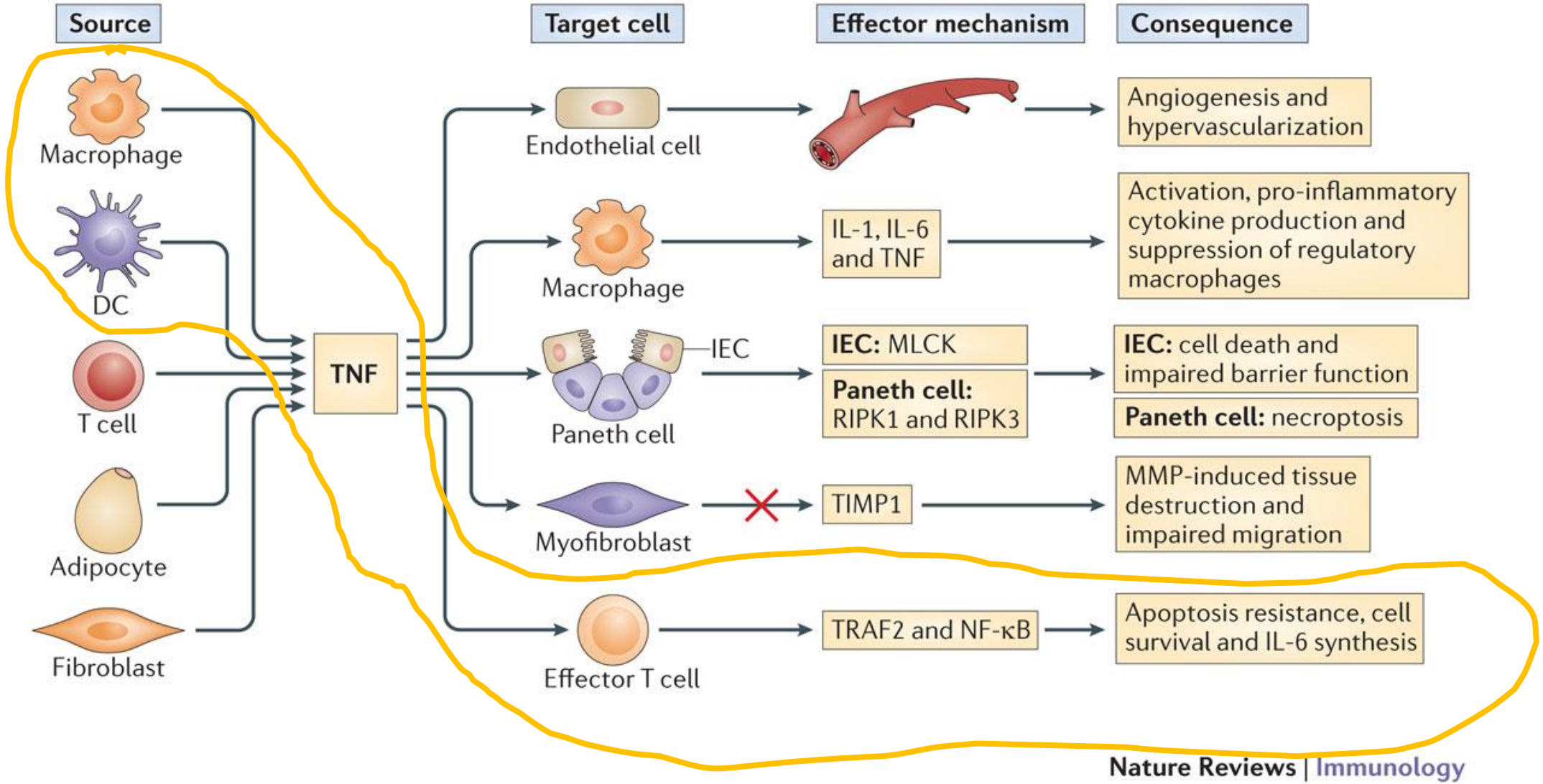
V-D-J region



https://www.antibodysociety.org/wordpress/wp-content/uploads/2015/12/Carter-IBC-INN-talk-Dec-2015-FINAL.pdf

CDRs: complementarity-defining regions

TNF-α



TNF: tumor necrosis factor

Neurath MF. Nat Rev Immunol 2014;14(5):329-42.

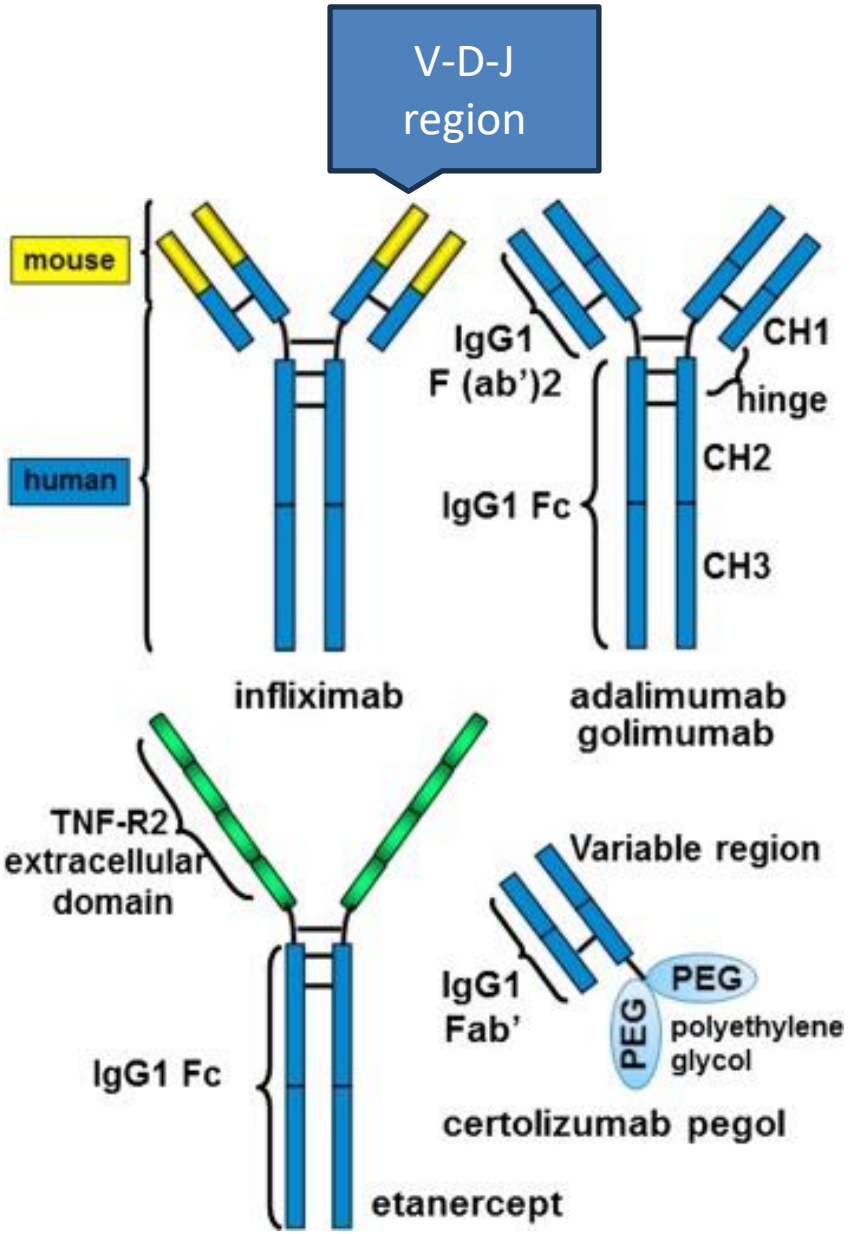
Various anti-TNF-α biologics

iv/sc infliximab

sc certolizumab
golimumab
adalimumab

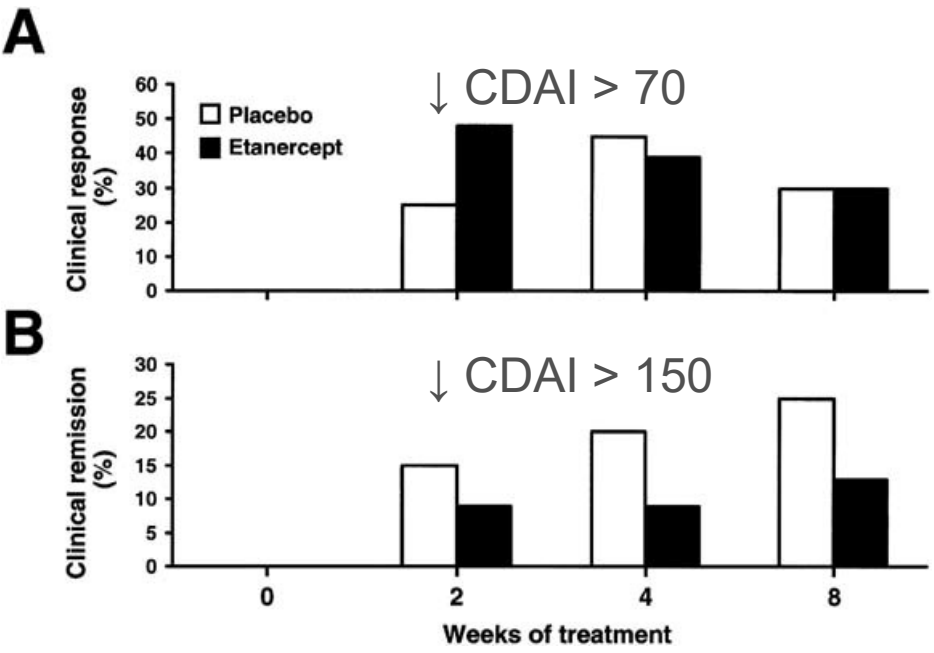
VS

etanercept



Mitoma H et al. Cytokine 2018;101:56-63.

Etanercept is not effective for Crohn's disease



Gastroenterology aga

CLINICAL RESEARCH | VOLUME 121, ISSUE 5, P1088-1094, NOVEMBER 2001

Etanercept for active Crohn's disease: A randomized, double-blind, placebo-controlled trial

William J. Sandborn • Stephen B. Hanauer • Seymour Katz • ... Therese Johnson • Nancy N. Diehl • Alan R. Zinsmeister • Show all authors

DOI: https://doi.org/10.1053/gast.2001.28674

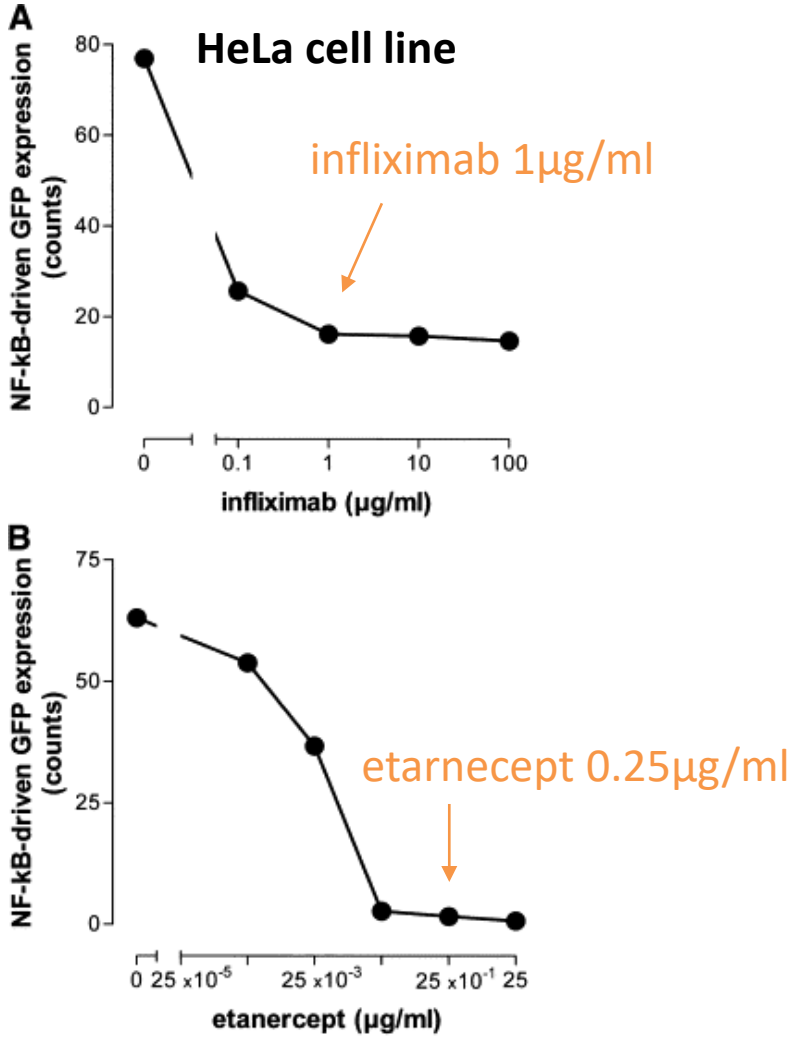
Abstract

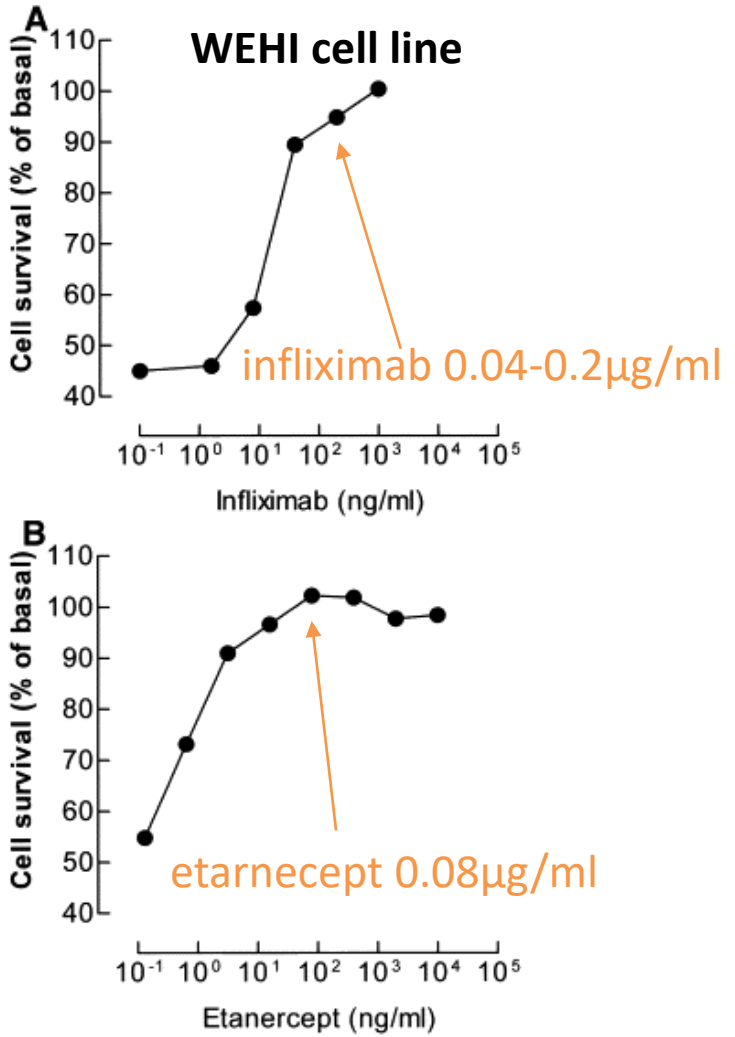
Background & Aims: We evaluated etanercept, a human soluble tumor necrosis factor receptor: Fc fusion protein, for the treatment of active Crohn's disease. **Methods:** Forty-three patients with moderate to severe Crohn's disease were enrolled in an 8-week placebo-controlled trial. Patients were randomized to subcutaneous etanercept 25 mg or placebo twice weekly. The primary outcome measure was clinical response at week 4, defined as a decrease in the baseline Crohn's Disease Activity Index score ≥70 points or a Crohn's Disease Activity Index score <150 points. **Results:** At week 4, 39% of etanercept-treated patients had clinical response as compared with 45% of placebo-treated patients ($P = 0.763$). The frequency of common adverse events including headache, new injection site reaction, asthenia, abdominal pain, Crohn's disease–related anemia, and skin disorders was similar in both groups. Likewise, the frequency of severe or serious adverse events was similar in both groups. **Conclusions:** Subcutaneous etanercept at a dose of 25 mg twice weekly is safe, but not effective, for the treatment of patients with moderate to severe Crohn's disease. The dose of etanercept administered in this study is that approved for rheumatoid arthritis. Higher doses or more frequent dosing may be required to attain a response in patients with active Crohn's disease.

GASTROENTEROLOGY 2001;121:1088-1094

Sandborn WJ. Gastroenterology 2001;121(5):1088-94.

Both infliximab and etanercept work against *soluble* TNF-α





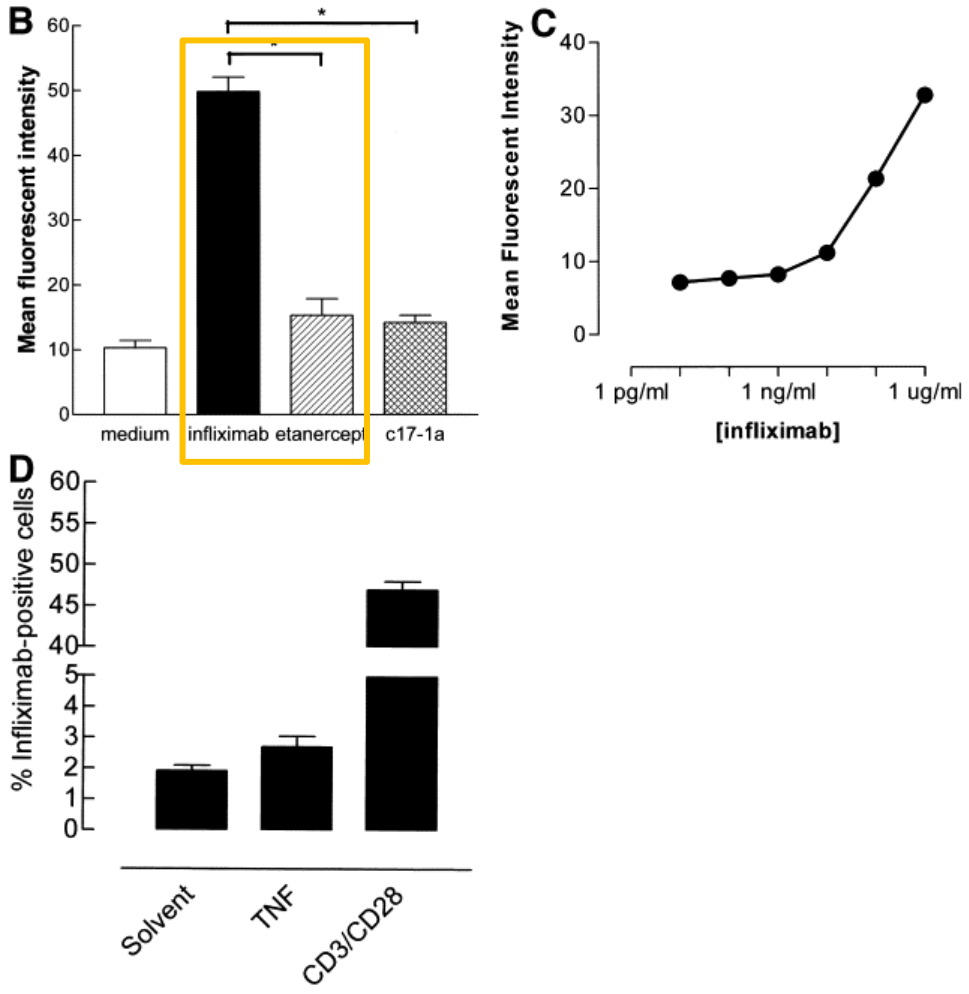
TNF-α-induced GFP expression in NF-κB reporter construct transfected cells

+ TNF-α 100pg/ml → 50% cell death

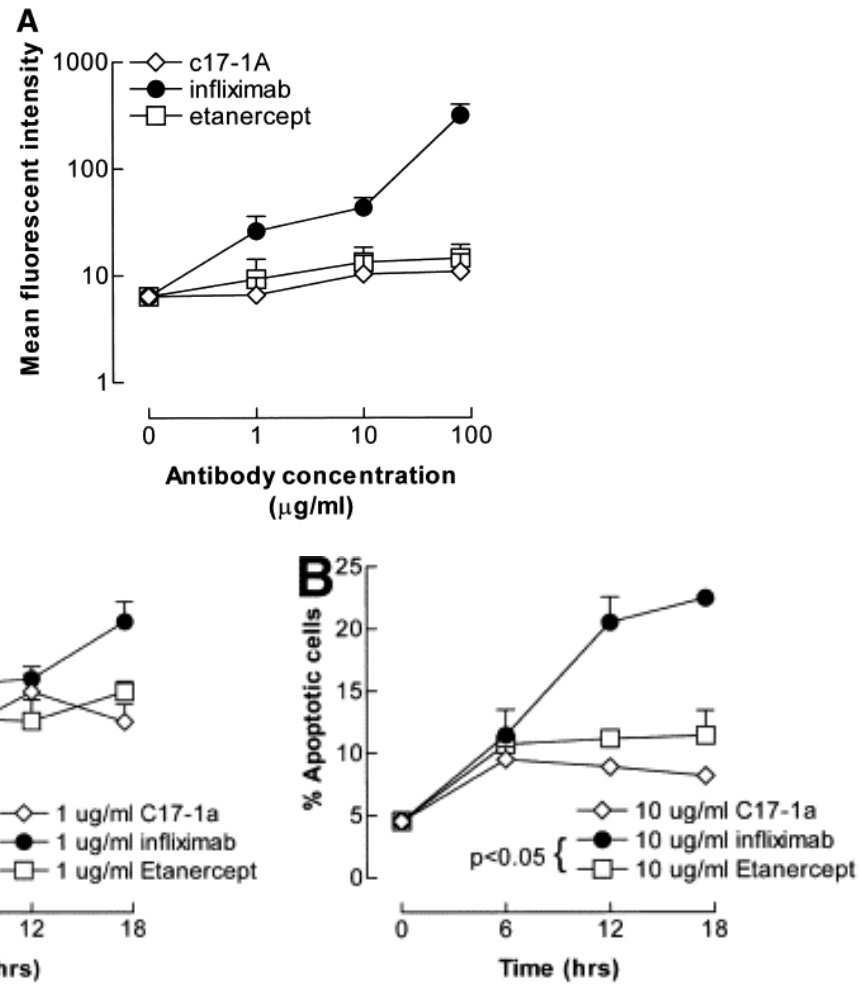
Van den Brande JMH et al. Gastroenterology 2003;124(7):1774-85.

… but, of the 2, only infliximab against *membrane-bound* TNF-α

Peripheral blood lymphocytes



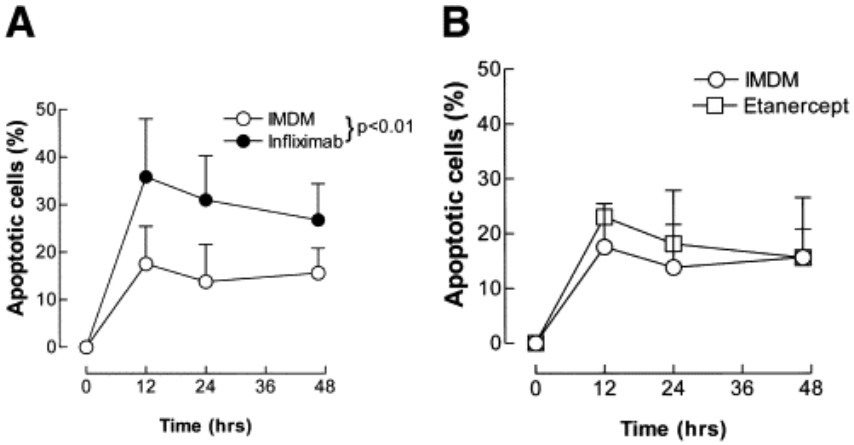
Lamina propria T cells

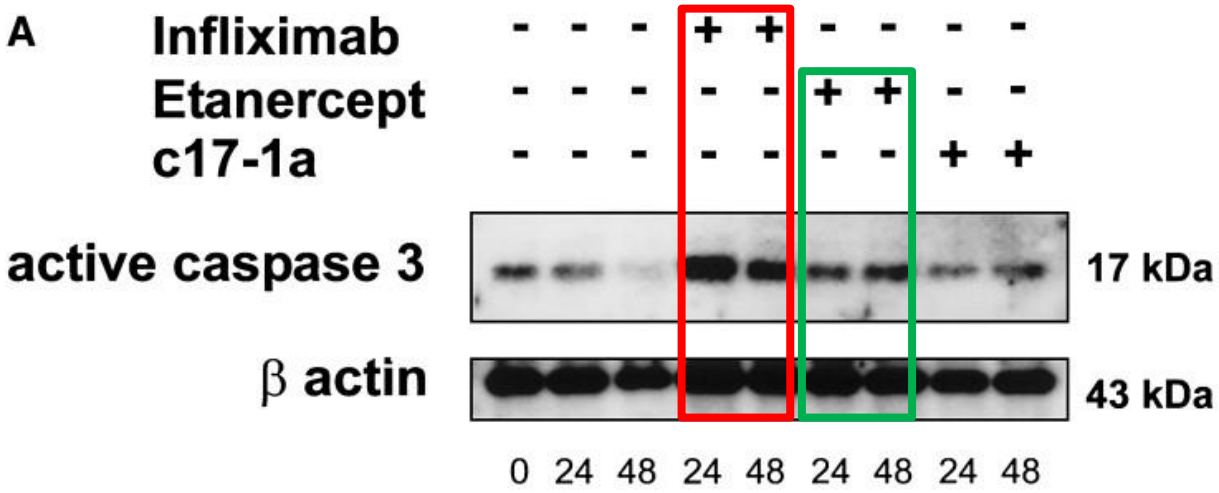


Van den Brande JMH et al. Gastroenterology 2003;124(7):1774-85.

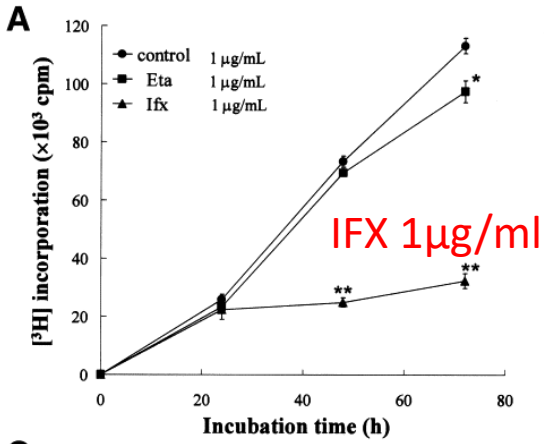
… and is effective in inducing T cell apoptosis

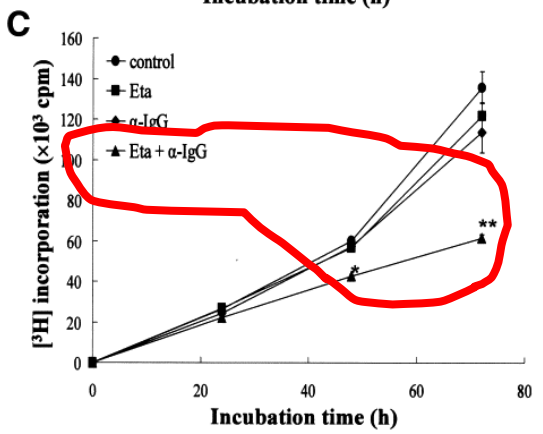
Peripheral blood lymphocytes





Jurkat



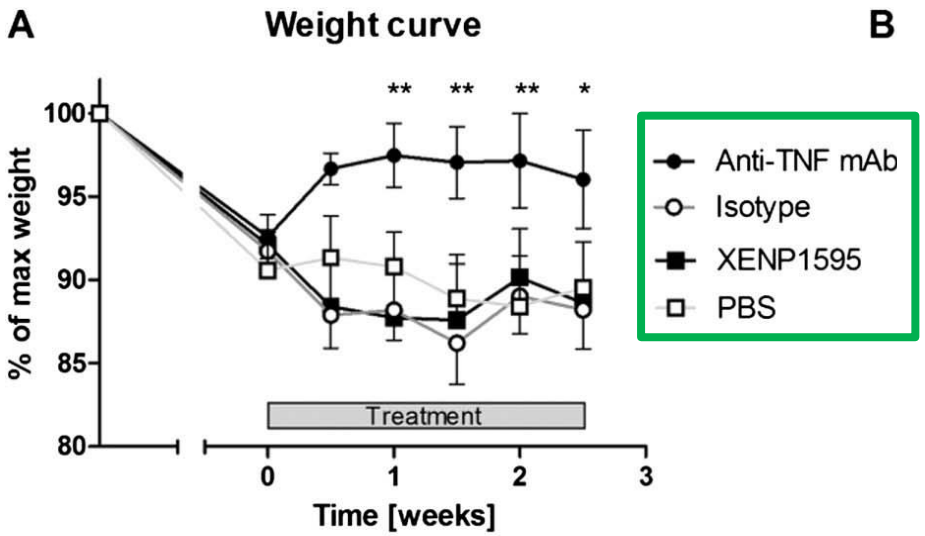


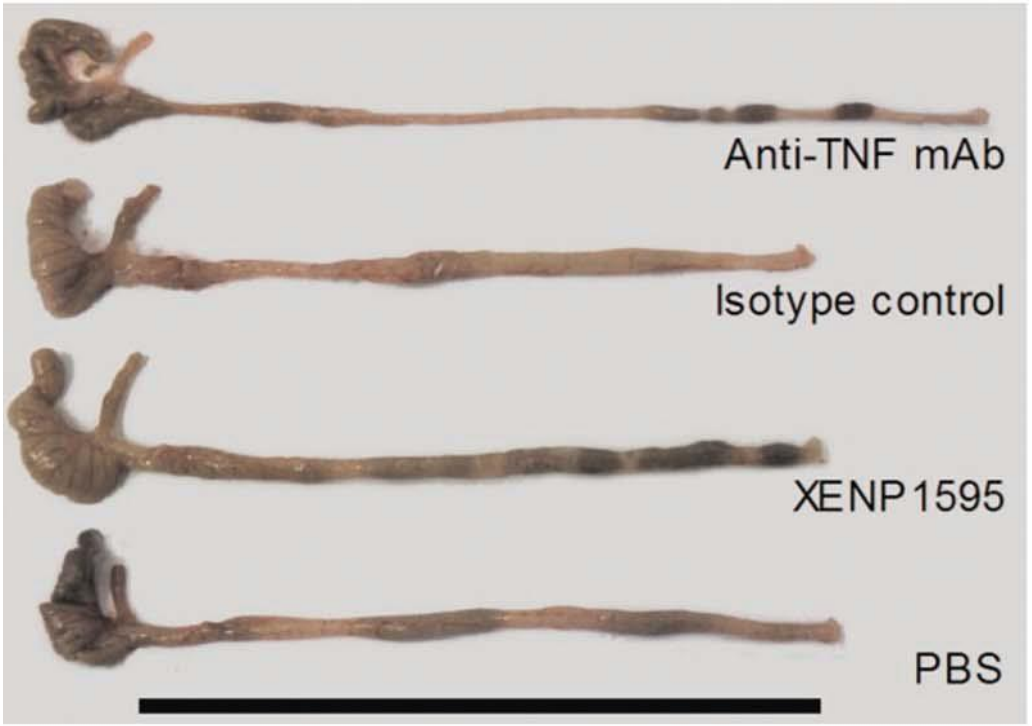
Van den Brande JMH et al. Gastroenterology 2003;124(7):1774-85.

Mitoma M et al. Gastroenterology 2005;128(2):376-92.

Membrane-bound, but not soluble, TNF-α matters *in vivo*

$CD4^{+}CD25^{-}CD45HB^{hi}$ into SCID mice

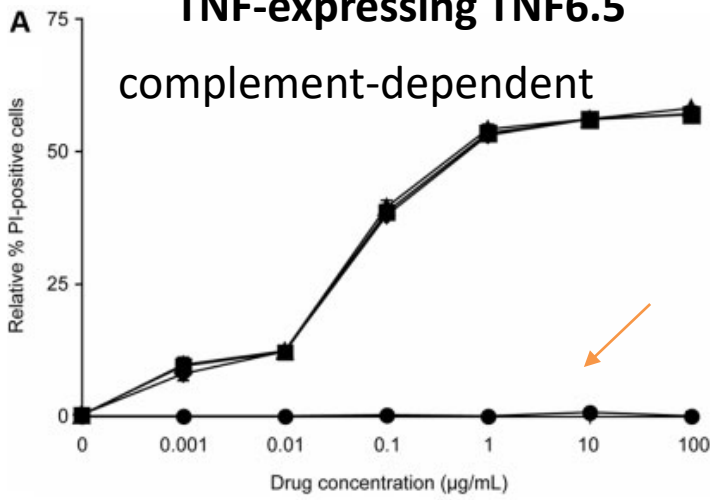


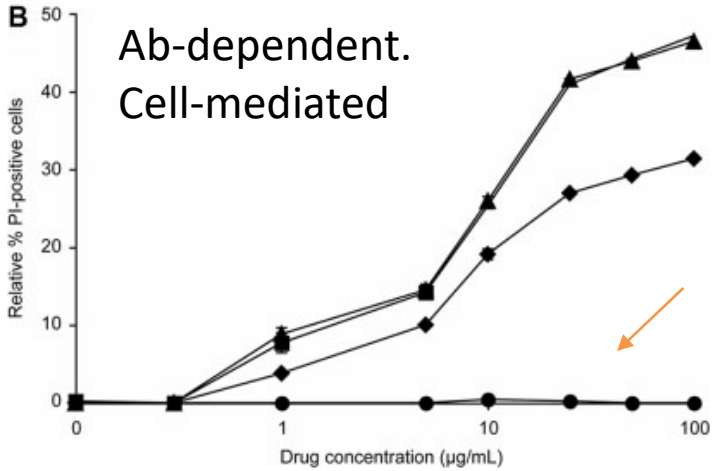


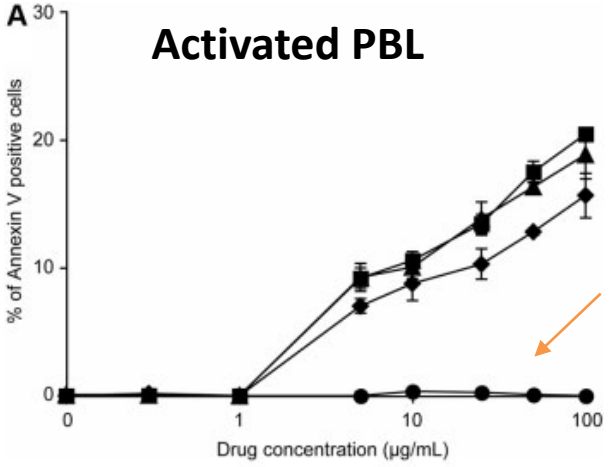
Perrier C et al. Inflamm Bowel Dis 2013;19(2):246-53.

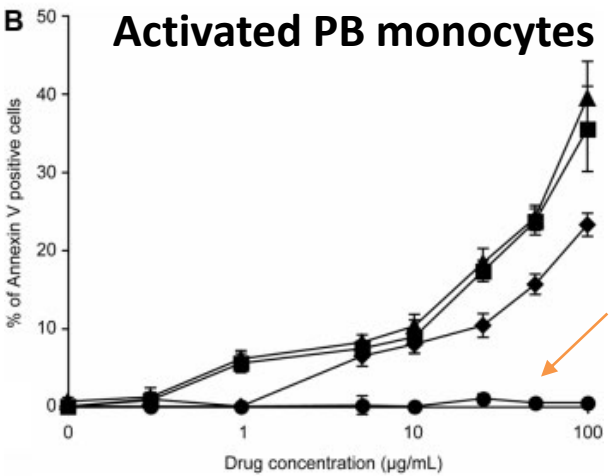
Certolizumab cannot induce apoptosis or degranulation

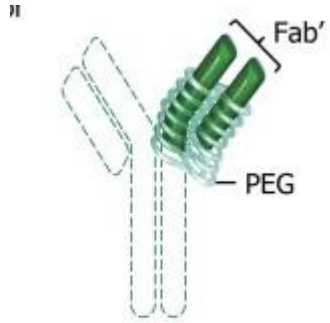
TNF-expressing TNF6.5





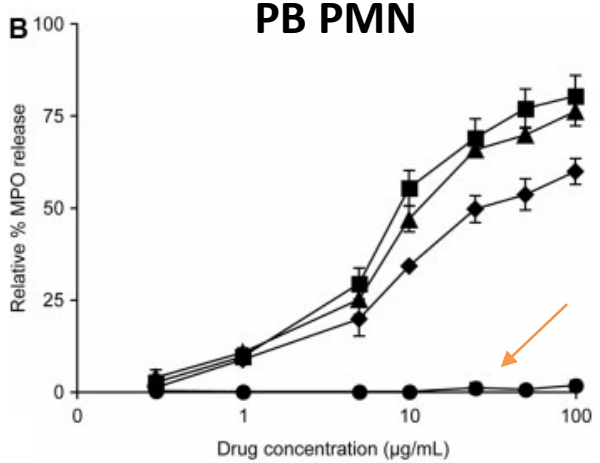






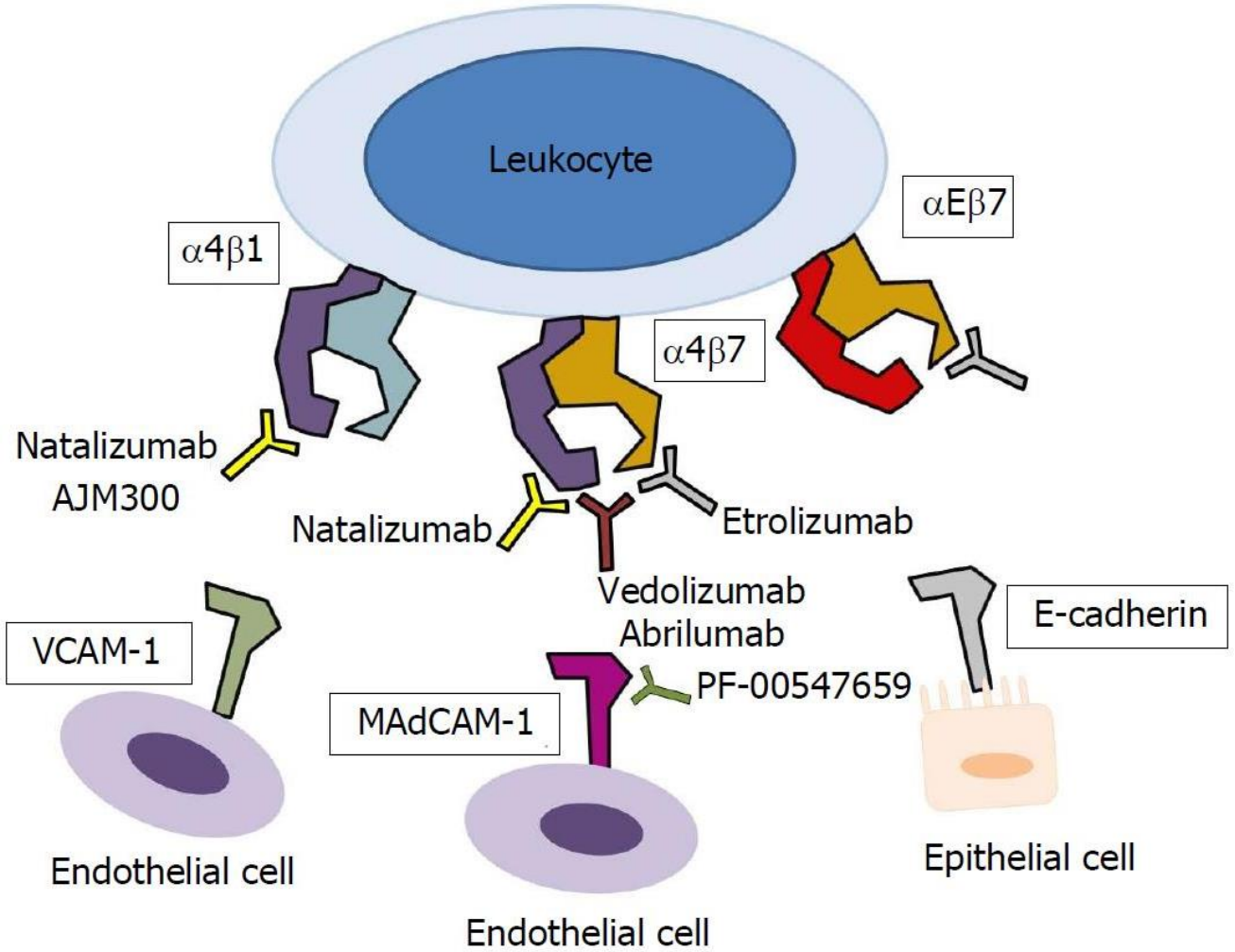
PEGylated
Fab' fragment/Fc-free

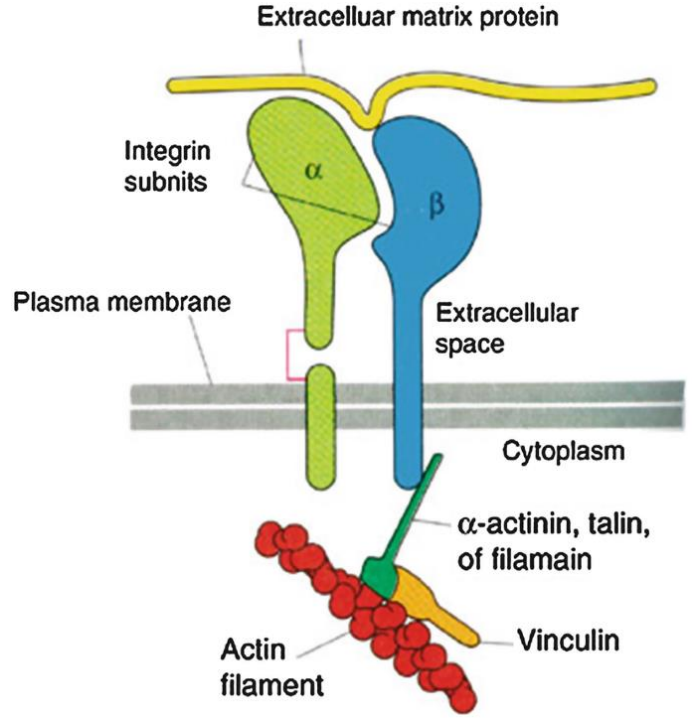
PB PMN



PB: peripheral blood

Anti-integrins

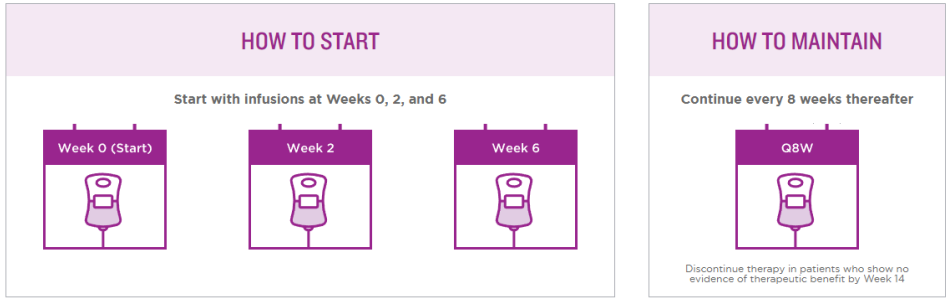




Gubatan J et al. Clin Exp Gastroenterol 2021;14:333-42.

GEMINI 1 trial for UC

iv



Induction

Table 2. Outcome Measures at Week 6 in the Trial of Induction Therapy.

Outcome	Placebo (N=149)	Vedolizumab (N=225)	Percentage-Point Difference (95% CI)*	P Value
	no. (%)			
Clinical response†	38 (25.5)	106 (47.1)	21.7 (11.6–31.7)	<0.001
Clinical remission‡	8 (5.4)	38 (16.9)	11.5 (4.7–18.3)	0.001
Mucosal healing§	37 (24.8)	92 (40.9)	16.1 (6.4–25.9)	0.001

Maintenance

Table 3. Outcome Measures in the Trial of Maintenance Therapy.

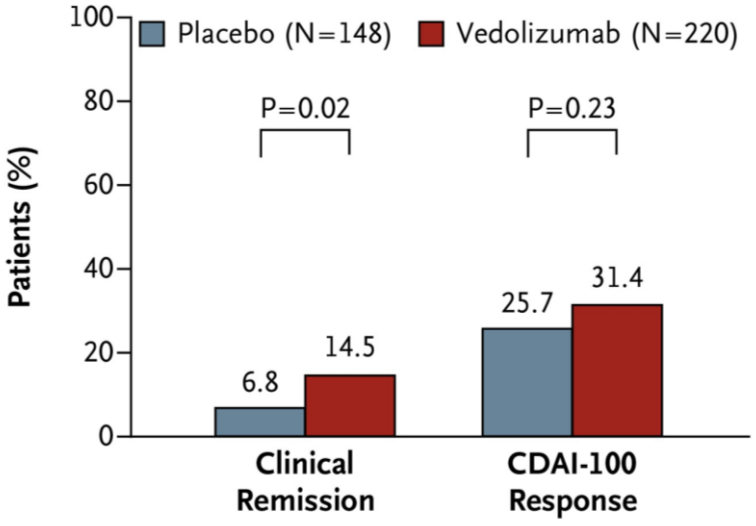
Outcome	Placebo (N=126)	Vedolizumab Every 8 Wk (N=122)	Vedolizumab Every 4 Wk (N=125)	Between-Group Difference*			
				Every 8 Wk vs. Placebo	P Value	Every 4 Wk vs. Placebo	P Value
	number/total number (percent)			*percentage points (95% CI)*		*percentage points (95% CI)*	
Clinical remission at wk 52	20/126 (15.9)	51/122 (41.8)	56/125 (44.8)	26.1 (14.9–37.2)	<0.001	29.1 (17.9–40.4)	<0.001
Durable clinical response†	30/126 (23.8)	69/122 (56.6)	65/125 (52.0)	32.8 (20.8–44.7)	<0.001	28.5 (16.7–40.3)	<0.001
Durable clinical remission‡	11/126 (8.7)	25/122 (20.5)	30/125 (24.0)	11.8 (3.1–20.5)	0.008	15.3 (6.2–24.4)	0.001
Mucosal healing at wk 52	25/126 (19.8)	63/122 (51.6)	70/125 (56.0)	32.0 (20.3–43.8)	<0.001	36.3 (24.4–48.3)	<0.001
Glucocorticoid-free remission at wk 52§	10/72 (13.9)	22/70 (31.4)	33/73 (45.2)	17.6 (3.9–31.3)	0.01	31.4 (16.6–46.2)	<0.001

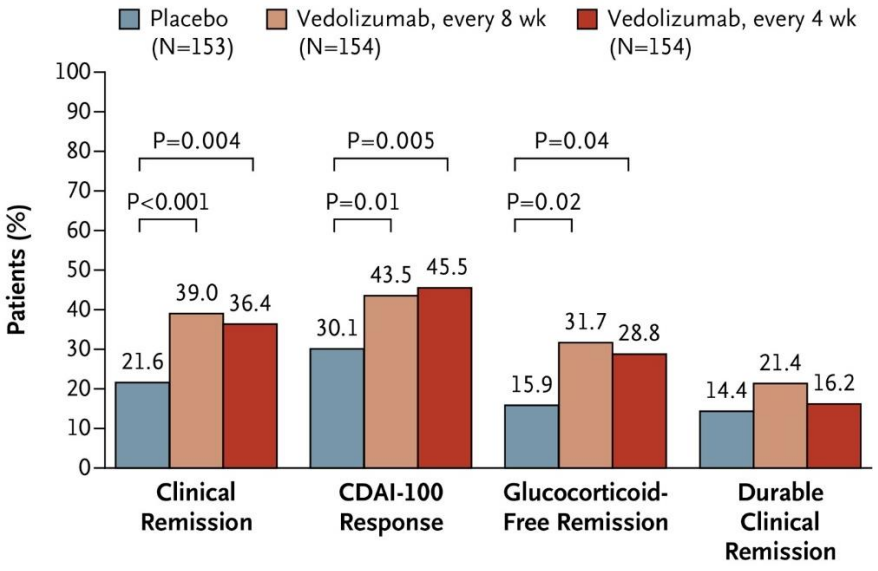
Adverse Events

- Headache
- Nasopharyngitis
- Upper respiratory tract infections

Feagan BG et al. New Engl J Med 2013;369(8):699-710.

Gemini 2 trial for CD



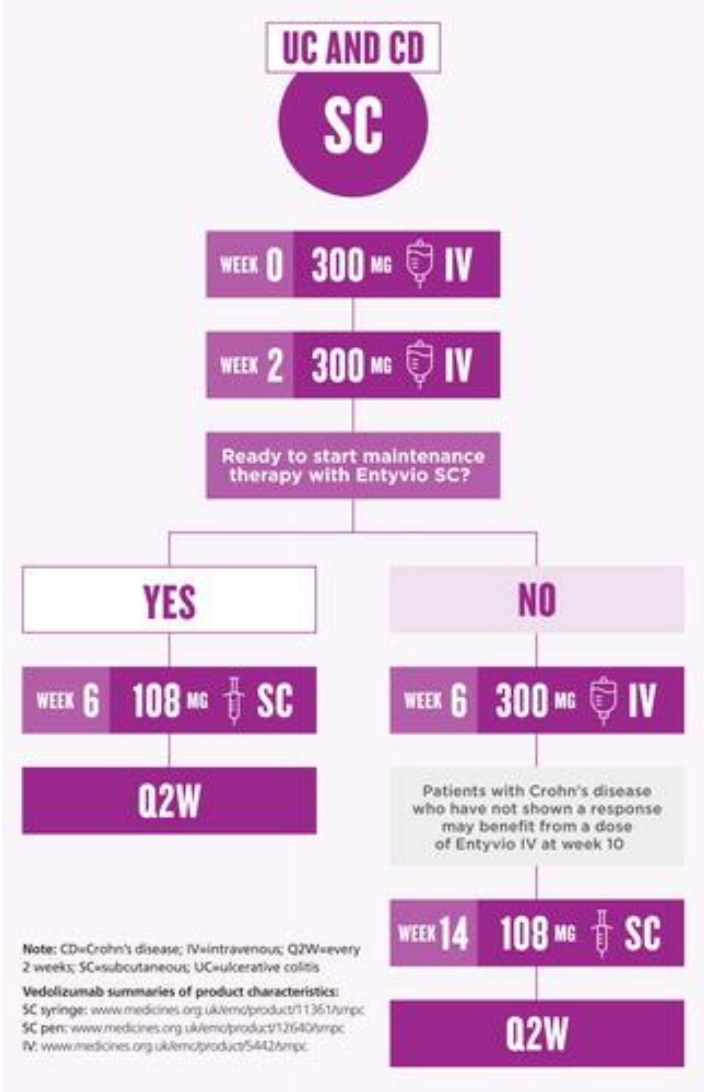


Sandborn WJ et al. New Engl J Med 2013;369(8):711-721.

However intensification to /4w may restore responsiveness in ~50% of IBD patients losing it…

Bouri S et al. Drug Ther Bull 2022;60(12):183-7.

sc



in development

more antibodies against integrins

- Abrilumab

new antibodies against integrin receptors

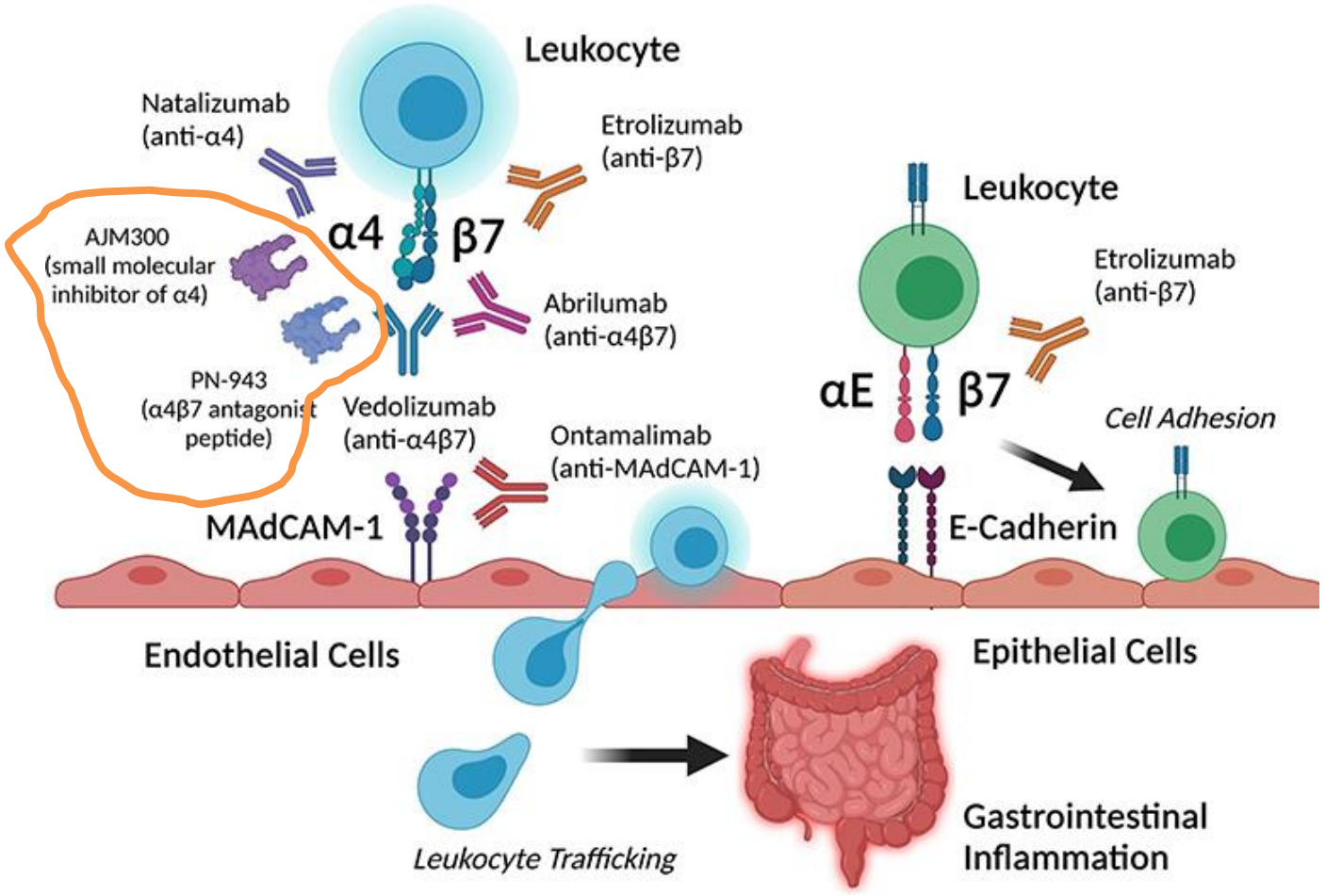
- Ontamalimab

small molecular inhibitors

- AJM300

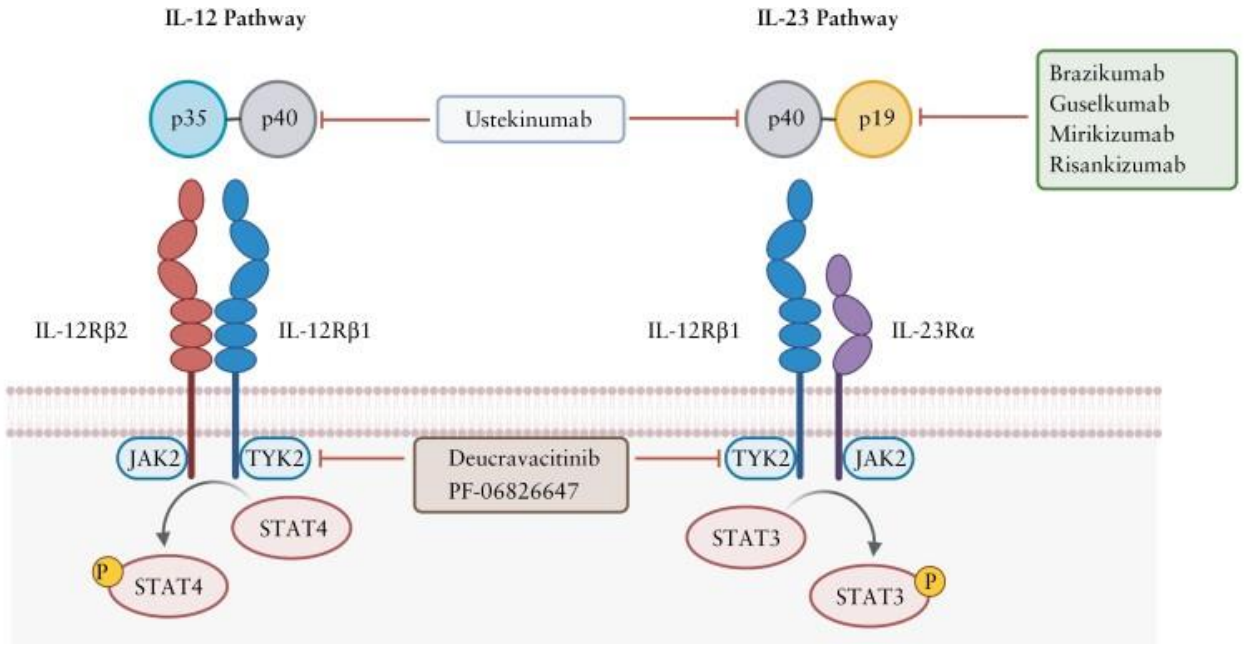
inhibitory peptides

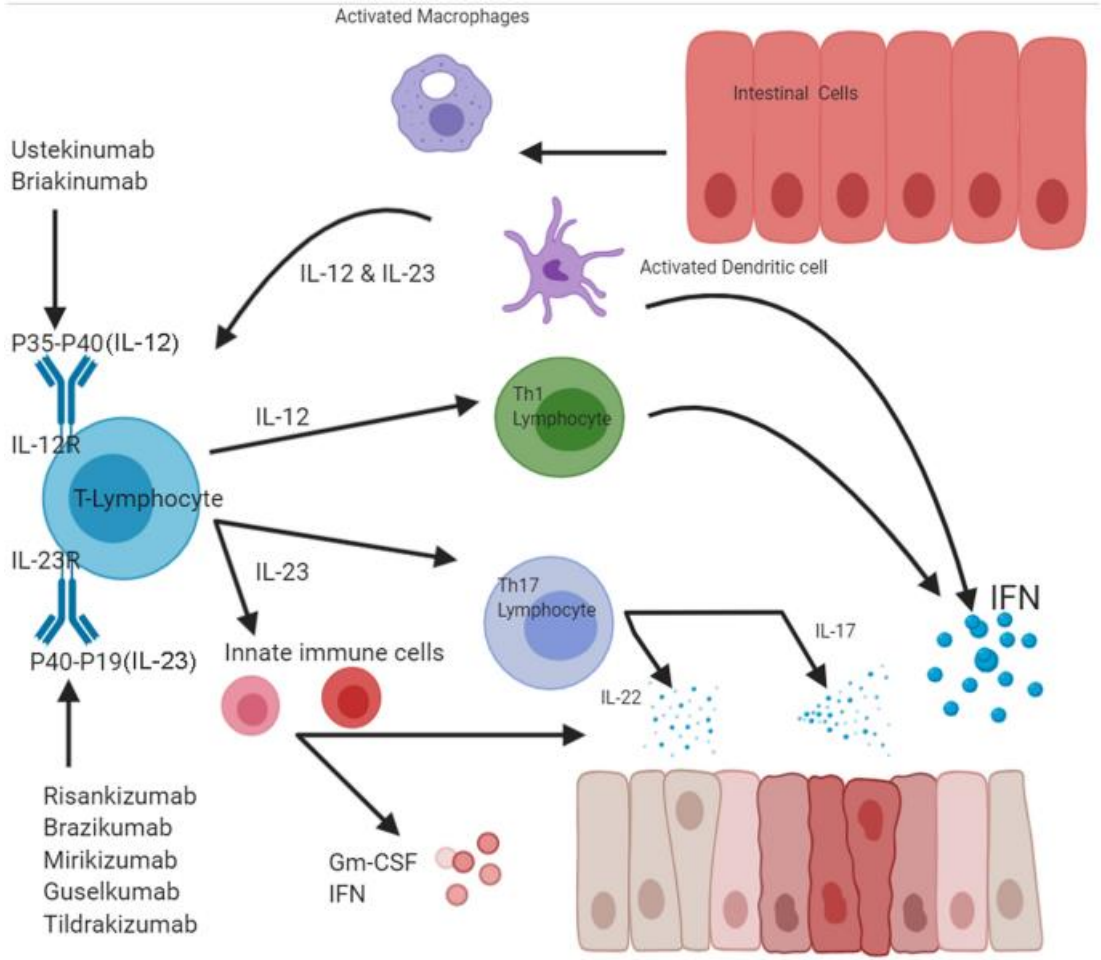
- PN-943



Gubatan J et al. Clin Exp Gastroenterol 2021;14:333-42.

IL-12/23



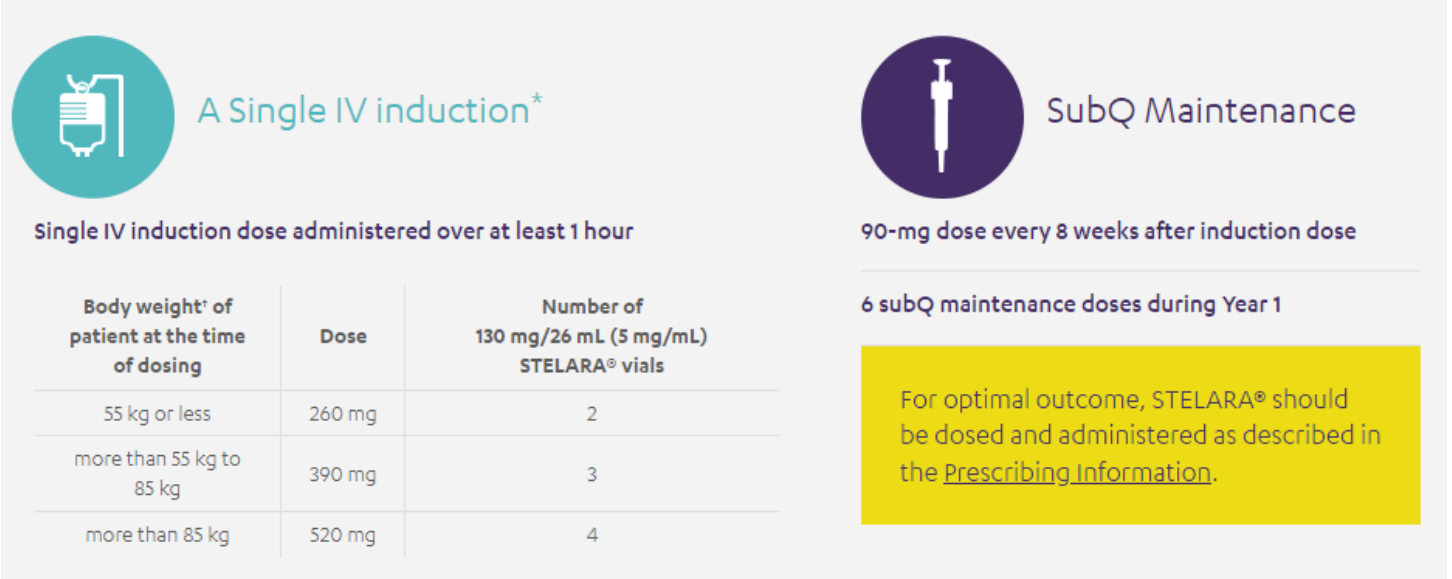


McDonald BD et al. JCC 2022;16(Suppl 2):ii42–53.

Almradi A et al. Biodrugs 2020;34(6):713-21.

Ustekinumab

- May be intensified to /4w



A Single IV induction*

Single IV induction dose administered over at least 1 hour

Body weight† of patient at the time of dosing	Dose	Number of 130 mg/26 mL (5 mg/mL) STELARA® vials
55 kg or less	260 mg	2
more than 55 kg to 85 kg	390 mg	3
more than 85 kg	520 mg	4

SubQ Maintenance

90-mg dose every 8 weeks after induction dose

6 subQ maintenance doses during Year 1

For optimal outcome, STELARA® should be dosed and administered as described in the Prescribing Information.

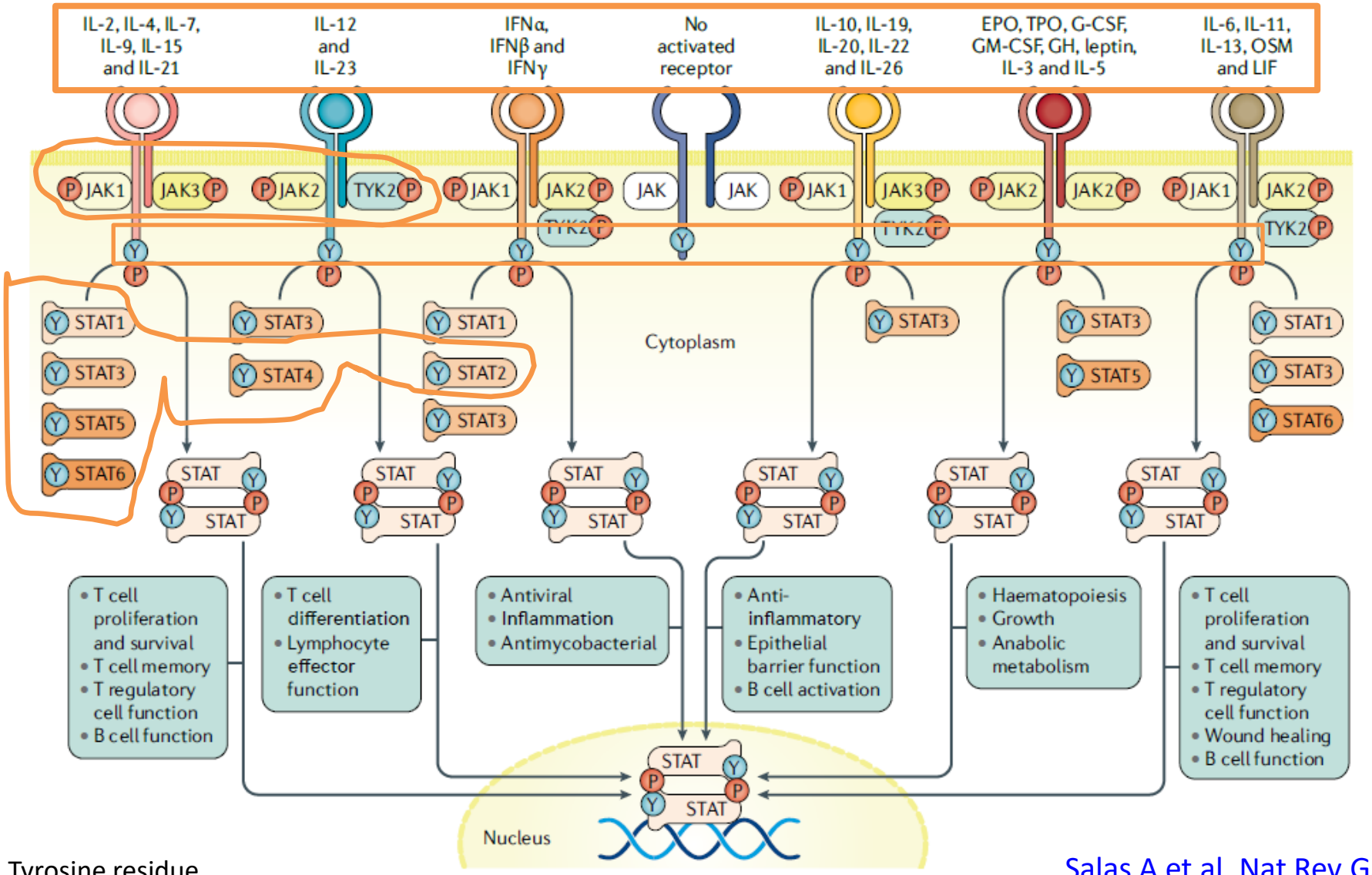
≠

Psoriasis, Psoriatic arthritis

45mg if BW<100kg, 90mg if >100kg

- More adverse effects in the placebo group

JAK – STAT pathway



Docked JAKs: auto- & trans- Pation

Docking site for STATs (common chain)

2nd intracellular messenger

Homo- or hetero- 2mers

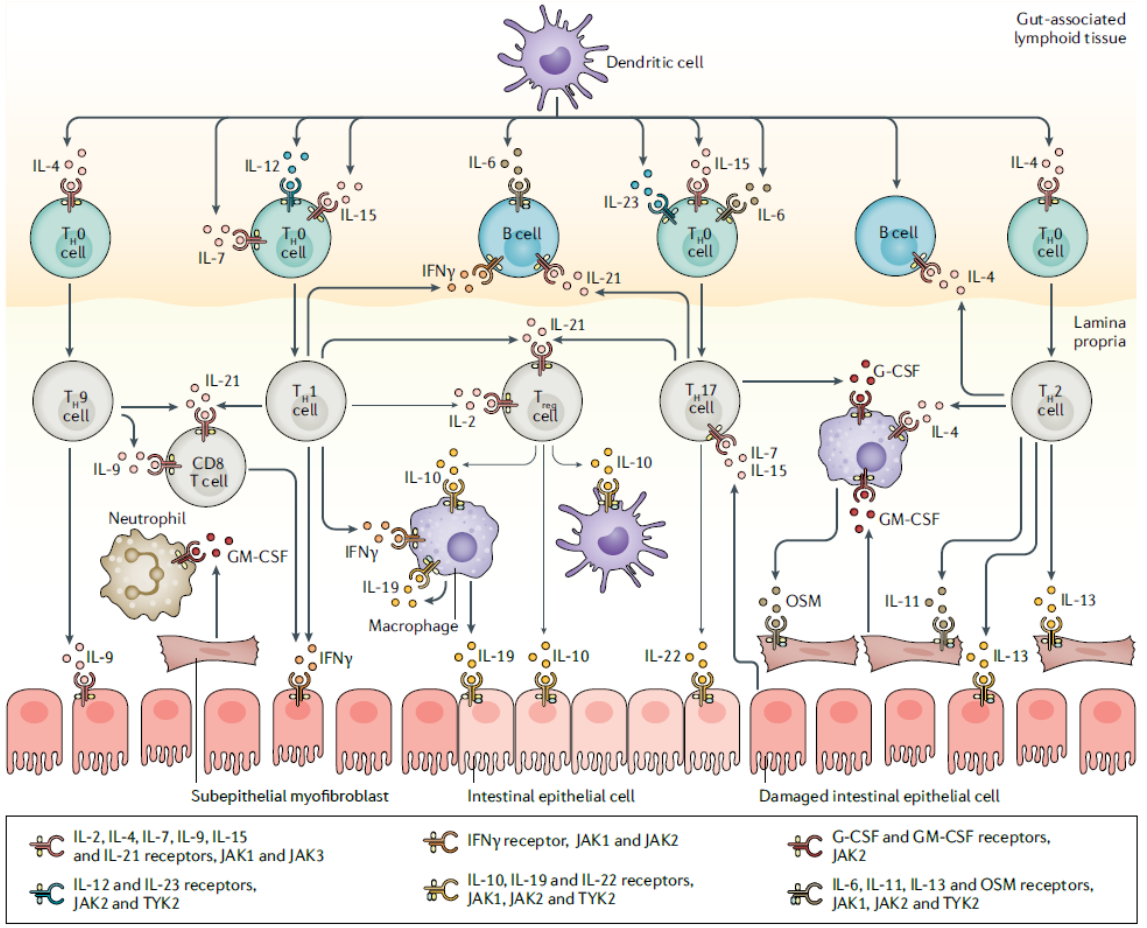
Y: Tyrosine residue

Salas A et al. Nat Rev Gastroenterol Hepatol 2020;17(6):323-337.

Pleiotropic effects

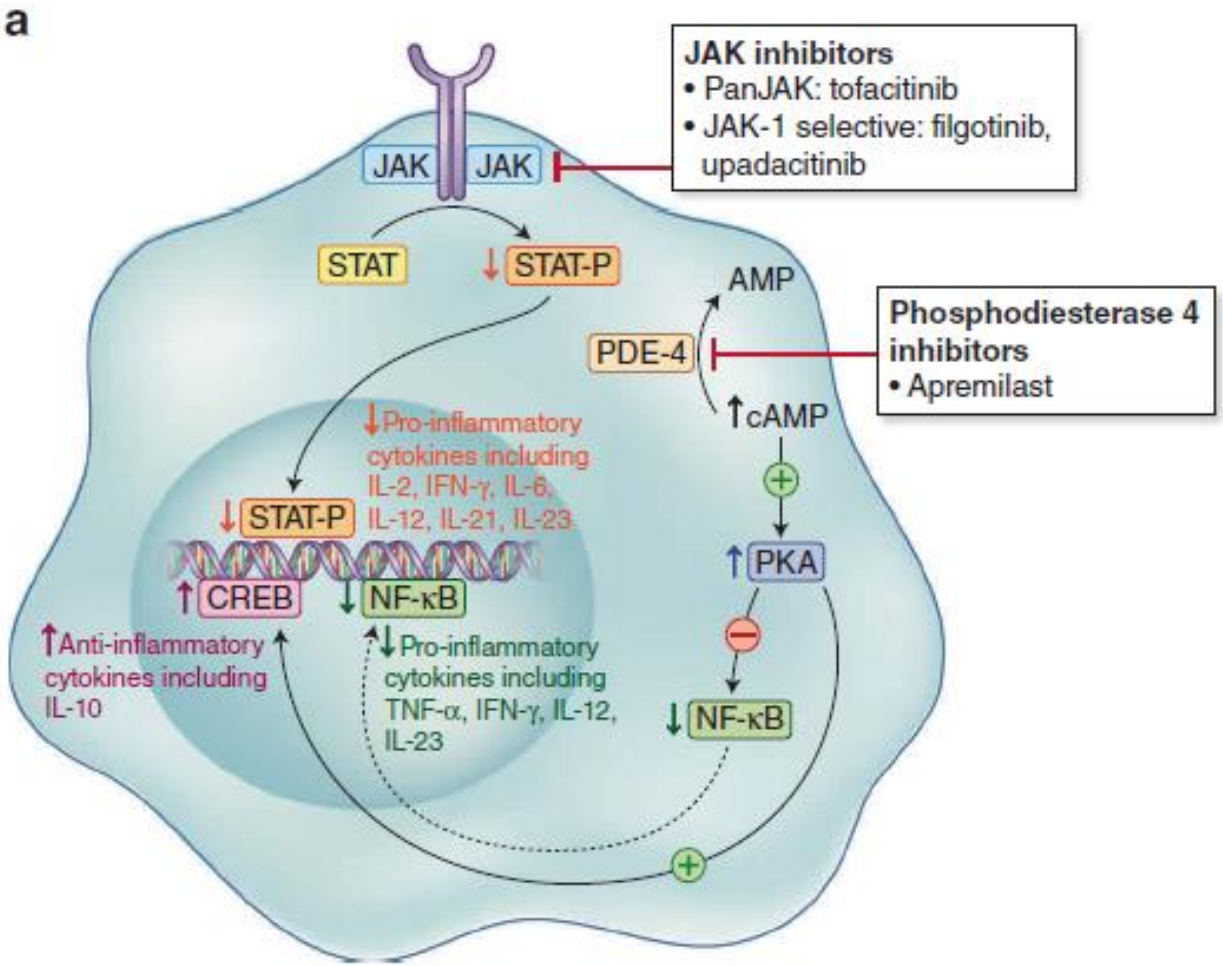
- highly variable, dependent on
  - cell
  - time
  - other simultaneous inputs
- on each and every cell

  not only cells of innate and adaptive immunity
- unpredictable



Salas A et al. Nat Rev Gastroenterol Hepatol 2020;17(6):323-337.

JAK inhibitors in IBD



Paramsothy S et al. Mucosal Immunol 2018;11(6):1558-70.

tofacitinib

Dosage

- 10mg x2 x2m or longer, then 5mg x2
- 10mg x2 may restore responsiveness
- 10mg x3 in ASUC

Table 2. Approved Xeljanz Dosing in the United States.

Indication	U.S. Approval	Dose
Rheumatoid Arthritis (RA)	2012	• Twice-daily 5 mg • Once-daily 11 mg extended release*
Psoriatic Arthritis (PsA)	2017	• Twice-daily 5 mg • Once-daily 11 mg extended release
Ulcerative Colitis (UC)	2018	• Twice-daily 10 mg (induction) • Twice-daily 5 or 10mg (maintenance)

*Xeljanx XR, approved in 2016

Adverse effects

- Infections: 2.9% vs 1.0% of the placebo group: pneumonia, herpes zoster infection, C. difficile, CMV
- ↑ hyperlipidemia

ASUC: acute severe ulcerative colitis

Upadacitinib for CD

Table 2. Primary and Key Secondary End Points under Multiplicity Control for Upadacitinib as Induction Therapy, According to FDA Requirements.*

End Point	U-EXCEL Induction Trial (12 wk)			U-EXCEED Induction Trial (12 wk)		
	Placebo (N=176)	Upadacitinib, 45 mg (N=350)	Adjusted Difference; P Value†	Placebo (N=171)	Upadacitinib, 45 mg (N=324)	Adjusted Difference; P Value†
Primary end points — % (95% CI)						
CDAI clinical remission‡	29.1 (22.4 to 35.8)	49.5 (44.2 to 54.8)	20.8 (12.7 to 28.8); P<0.001	21.1 (14.9 to 27.2)	38.9 (33.6 to 44.2)	17.9 (10.0 to 25.8); P<0.001
Endoscopic response§	13.1 (8.1 to 18.0)	45.5 (40.3 to 50.8)	33.0 (26.2 to 39.9); P<0.001	3.5 (0.8 to 6.3)	34.6 (29.4 to 39.8)	31.2 (25.5 to 37.0); P<0.001
Clinical response — % (95% CI)§§						
At wk 2	20.4 (14.4 to 26.5)	32.2 (27.3 to 37.1)	11.7 (4.2 to 19.2); P=0.002	12.4 (7.4 to 17.4)	33.2 (28.0 to 38.3)	20.7 (13.7 to 27.8); P<0.001
At wk 12	37.3 (30.1 to 44.5)	56.6 (51.4 to 61.8)	19.8 (11.3 to 28.4); P<0.001	27.5 (20.8 to 34.2)	50.5 (45.1 to 56.0)	22.8 (14.4 to 31.2); P<0.001
CDAI clinical remission at wk 4 — % (95% CI)‡	26.7 (20.2 to 33.3)	37.1 (32.1 to 42.2)	10.8 (2.9 to 18.6); P=0.007	17.7 (11.9 to 23.4)	29.6 (24.7 to 34.6)	12.1 (4.7 to 19.5); P=0.001

Loftus EV Jr et al. N Engl J Med 2023;388(21):1966-80.

Upadacitinib

Table 3. Primary and Secondary End Points under Multiplicity Control for Upadacitinib as Maintenance Therapy, According to FDA Requirements.*

End Point, Wk 52	Placebo (N=165)	Upadacitinib, 15 mg (N=169)	Adjusted Difference vs. Placebo; P Value†	Upadacitinib, 30 mg (N=168)	Adjusted Difference vs. Placebo; P Value†
Primary end points — % (95% CI)					
CDAI clinical remission‡	15.1 (9.6 to 20.6)	37.3 (30.0 to 44.6)	23.7 (15.2 to 32.1); P<0.001	47.6 (40.1 to 55.2)	32.8 (23.9 to 41.6); P<0.001
Endoscopic response§	7.3 (3.3 to 11.2)	27.6 (20.8 to 34.4)	21.0 (13.6 to 28.4); P<0.001	40.1 (32.7 to 47.6)	33.7 (26.0 to 41.3); P<0.001
Ranked secondary end points¶					
SF–APS clinical remission — % (95% CI)‖	14.4 (9.0 to 19.8)	35.5 (28.3 to 42.7)	21.9 (13.7 to 30.0); P<0.001	46.4 (38.9 to 54.0)	31.8 (23.2 to 40.3); P<0.001
Clinical response — % (95% CI)**	15.2 (9.7 to 20.6)	41.4 (34.0 to 48.8)	27.1 (18.3 to 35.8); P<0.001	51.2 (43.6 to 58.7)	36.4 (27.5 to 45.2); P<0.001
Endoscopic remission — % (95% CI)††	5.5 (2.0 to 9.0)	19.1 (13.1 to 25.0)	14.4 (7.7 to 21.0); P<0.001	28.6 (21.8 to 35.5)	23.6 (16.1 to 31.0); P<0.001
Glucocorticoid-free CDAI clinical remission among all patients — % (95% CI)‡‡	14.5 (9.1 to 19.9)	36.7 (29.4 to 44.0)	23.8 (15.5 to 32.1); P<0.001	46.4 (38.9 to 54.0)	32.2 (23.4 to 40.9); P<0.001
Deep remission — % (95% CI)§§	3.7 (0.8 to 6.5)	14.8 (9.5 to 20.2)	12.2 (6.3 to 18.1); P<0.001	23.2 (16.8 to 29.6)	19.8 (13.0 to 26.6); P<0.001

Loftus EV Jr et al. N Engl J Med 2023;388(21):1966-80.

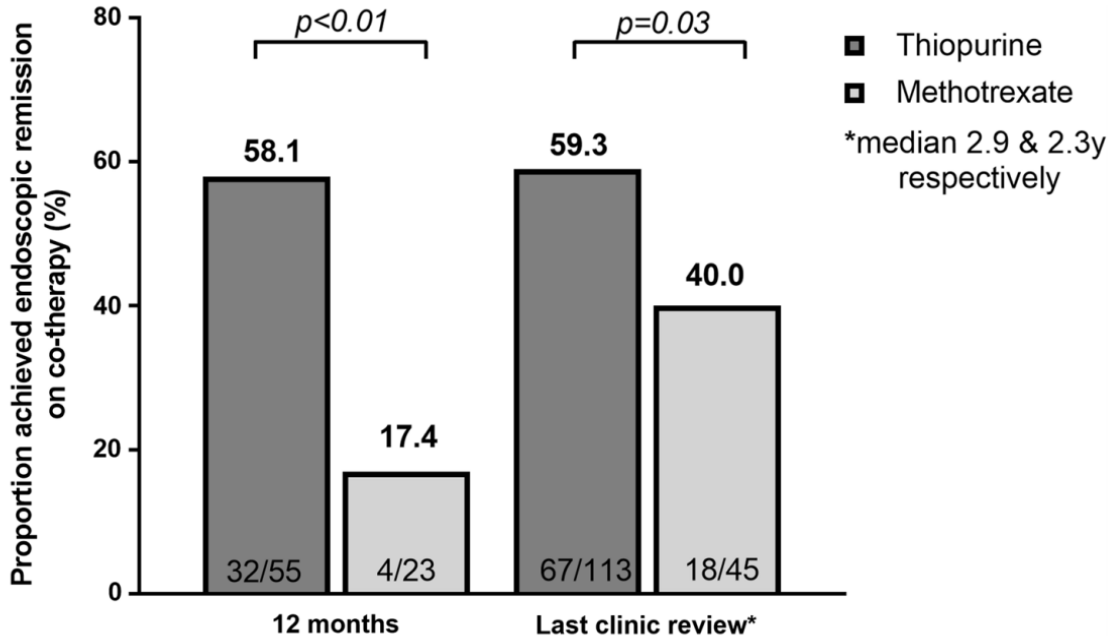
IMMs: AZA superior to MTX

- AZA: UC > CD
- TPMT activity beforehand in children

<u>Adverse effects</u>

- dose-dependent (allopurinol trick)
  - ✓ GI intolerance
  - ✓ Neutropenia (methyl)
- idiosyncratic
  - ✓ Pancreatitis (S…)
  - ✓ Fever
  - ✓ Hepatitis (methyl...)

– How about:
  - ✓ EBV IgG (-) young males (hepatosplenic lymphoma?)
  - ✓ > 60y (neoplasia?)
  - ✓ History of malignancy ?

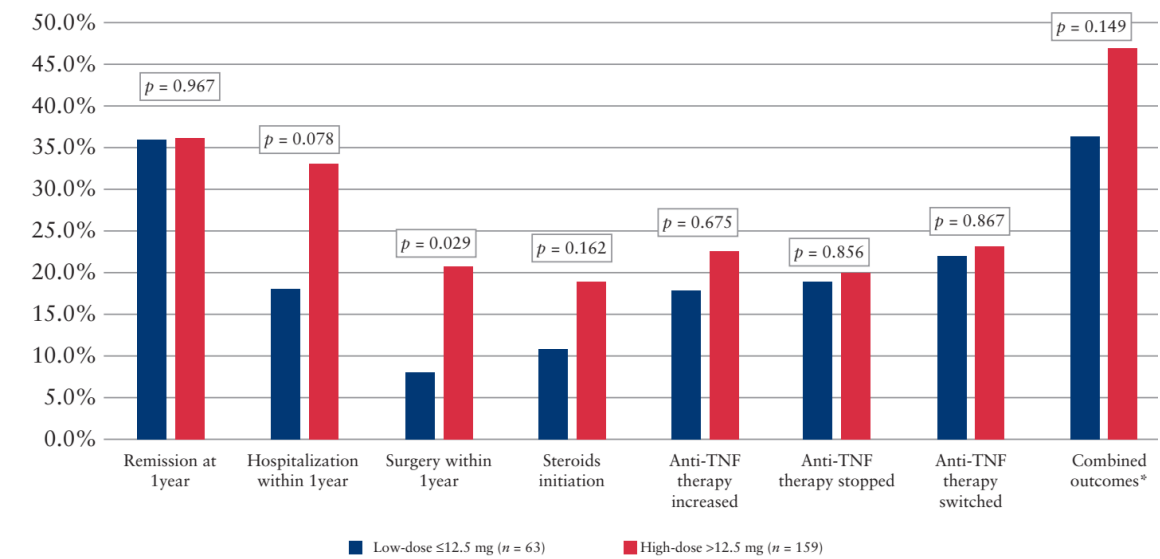


AZA: azathioprine; IMM: immunomodulator; MTX: methotrexate

Vasudevan A et al. Dig Dis Sci 2019;64(6):1622-31.

MTX

- CD: NNT 5
- Inhibits de no synthesis of nucleosides
- **Blocks ICAR transformylase -→ … → <u>↑ adenosine</u>**
- Full activity within 4-6w
- subcutaneously vs per os
- To be used
  - ✓ with anti-TNFα in case of AZA intolerance/adverse effects/Ca
  - ✓ to reduce IFX immunogenicity (equipotent to AZA)
  - ✓ in TPMT homozygotes



Comparison of safety [a] and efficacy [b] outcomes between low-dose MTX and high-dose MTX combination therapy.

- Nausea
- Hepatotoxicity
- Myelosuppression
- Pneumonitis (irreversible!)

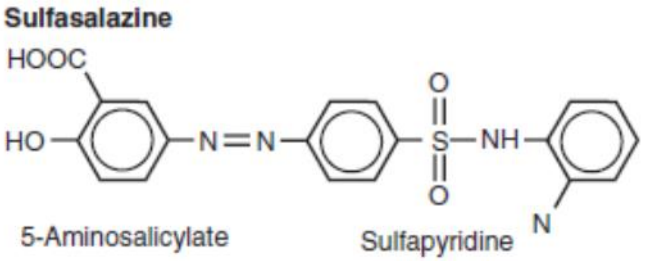
- Contraception!
- No lactation!

Borren NZ et al. Journal Crohns Colitis 2019;13(8):990-5.

UC: rarely needed to build up on salicylate treatment

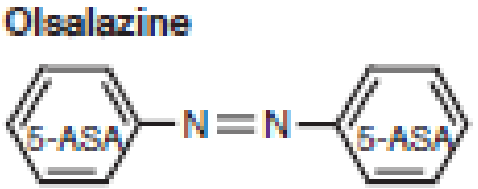
- Salicylates alone are sufficient for 70-90% of UC patients (mild-moderate disease)

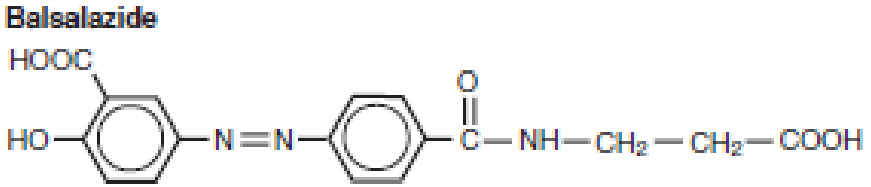
<u>Sulphasalazine</u>



- 5-Aminosalicylate (5-ASA)
  - ✓ principal therapeutic moiety

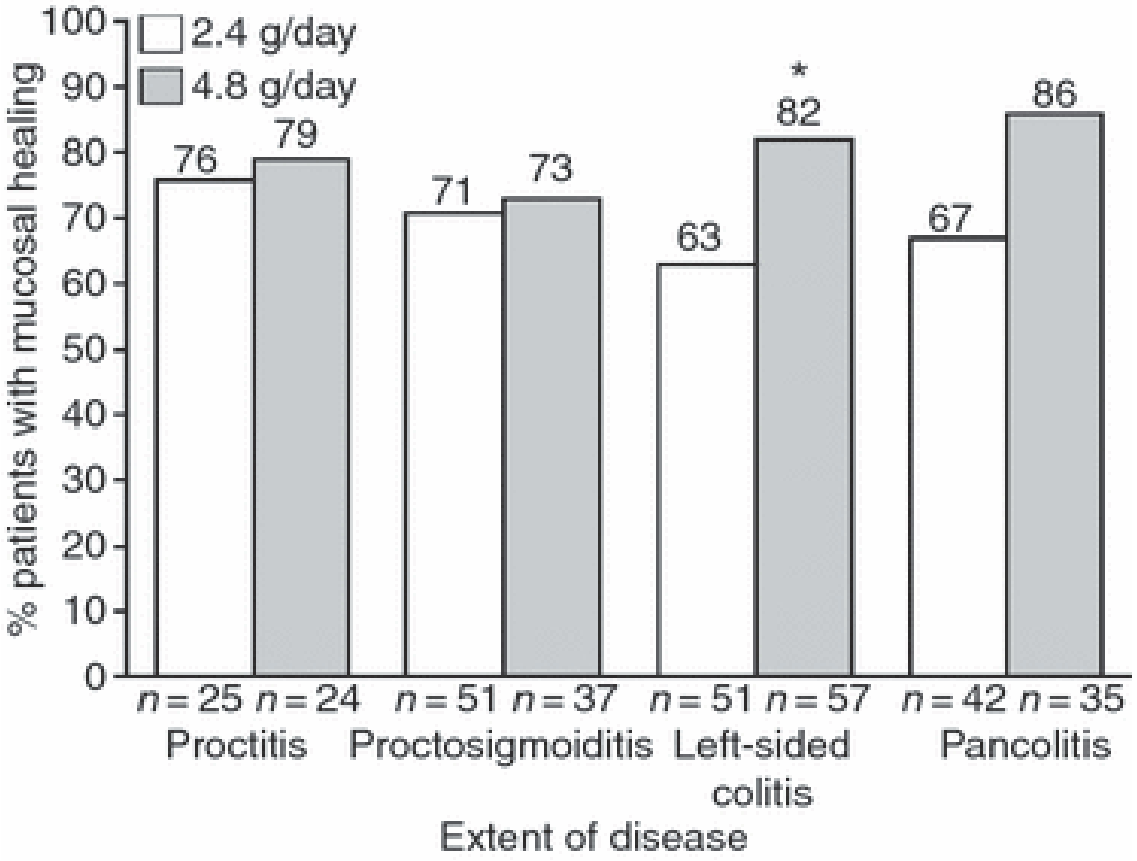
- Sulfapyridine
  - ✓ inactive carrier to prevent absorption in the small intestine → 90% reaches the colon
  - ✓ colon: azoreductase by anaerobes liberates 5-ASA releasing it to the colon



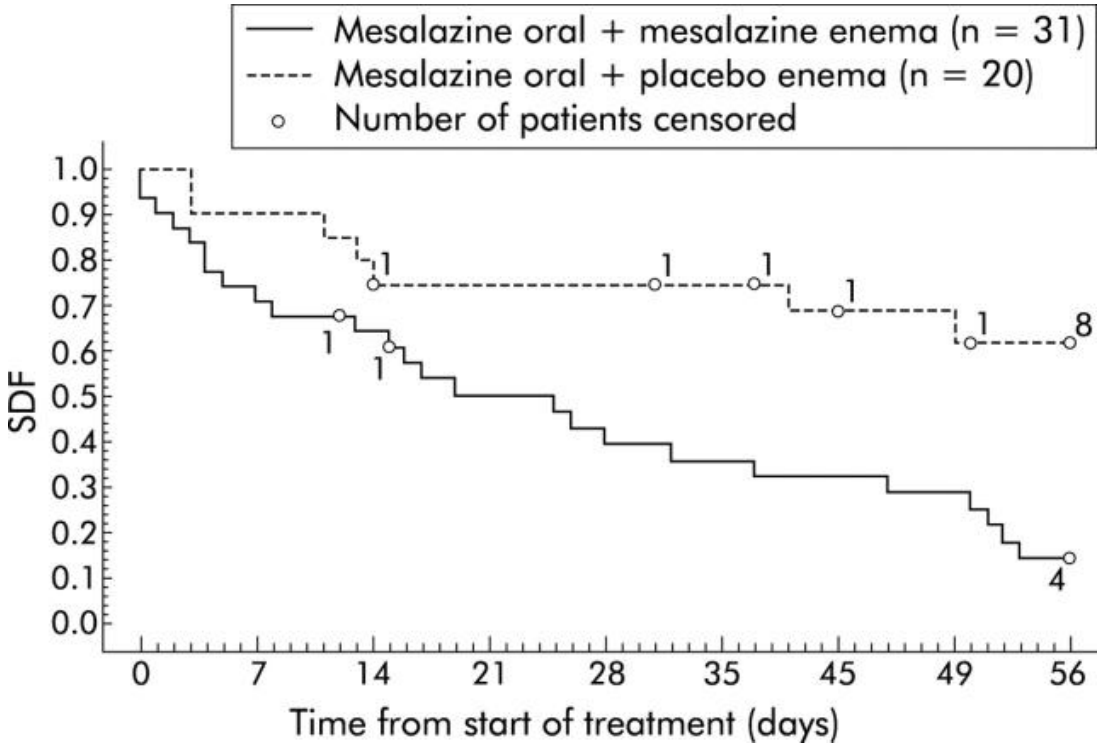


Salicylates: efficacy

Week 6



Cessation of bleeding



Once daily dosage - No lowering in remission

Lichtenstein GR et al. Aliment Pharmacol Ther 2011;33(6):672-8

Marteau P et al. Gut 2005;54(7):960-5.

Corticosteroids

Systemic

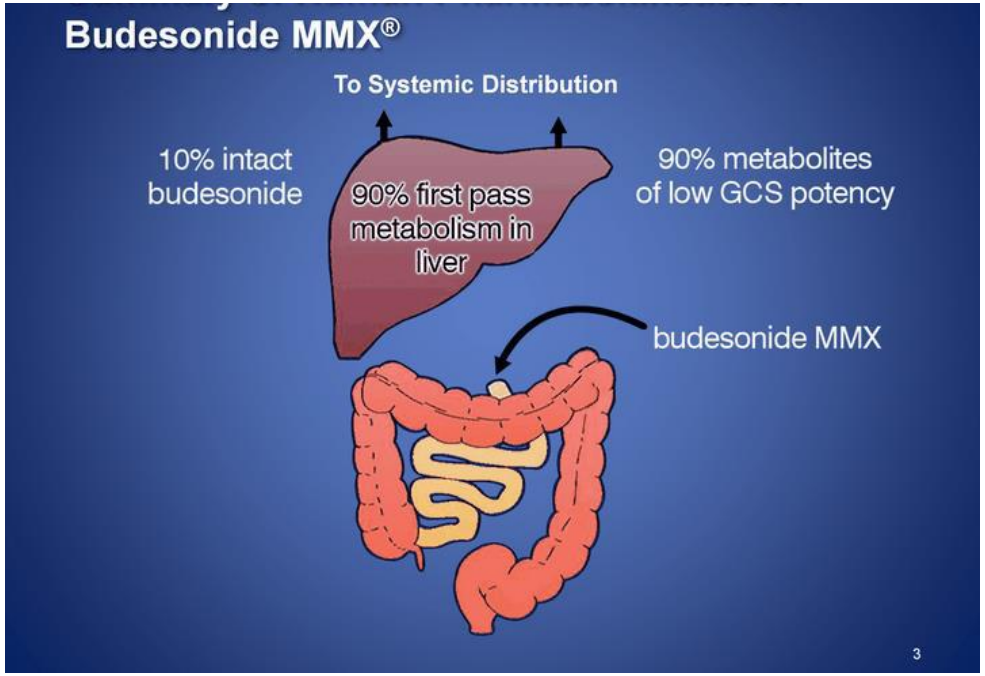
- Prednisolone 0.75-1mg/kg → tapering / 5-10mg / 1-2w
- No more than 1 course / year !

Bioavailability confined to portal vein

- Budecol@, Budenofalk Uno @
  - ✓ Eudragit
  - ✓ pH > 6.4
  - ✓ → distal ileum → CD
- Cortiment
  - ✓ MMX
  - ✓ → colon → UC

Local

- Less effective than salicylates for UC
- Add-on effect statistically significant



Take-home messages

- Anti-TNF biologics “tailored” to disease
- Dosage: Induction ≠ Maintenance
  time-dosage
- Gut specific medications
  - anti-integrins
  - Budesonide
- Extraintestinal manifestations
- Increasing % of elderly patients

→multidisciplinary meetings necessary for educated therapeutic decisions

Ευχαριστώ για την προσοχή σας!