Advanced Drugs in Inflammatory Bowel Disease

Dr Gillian Gaskin

Gastroenterology Fellow

Inkosi Albert Luthuli Hospital

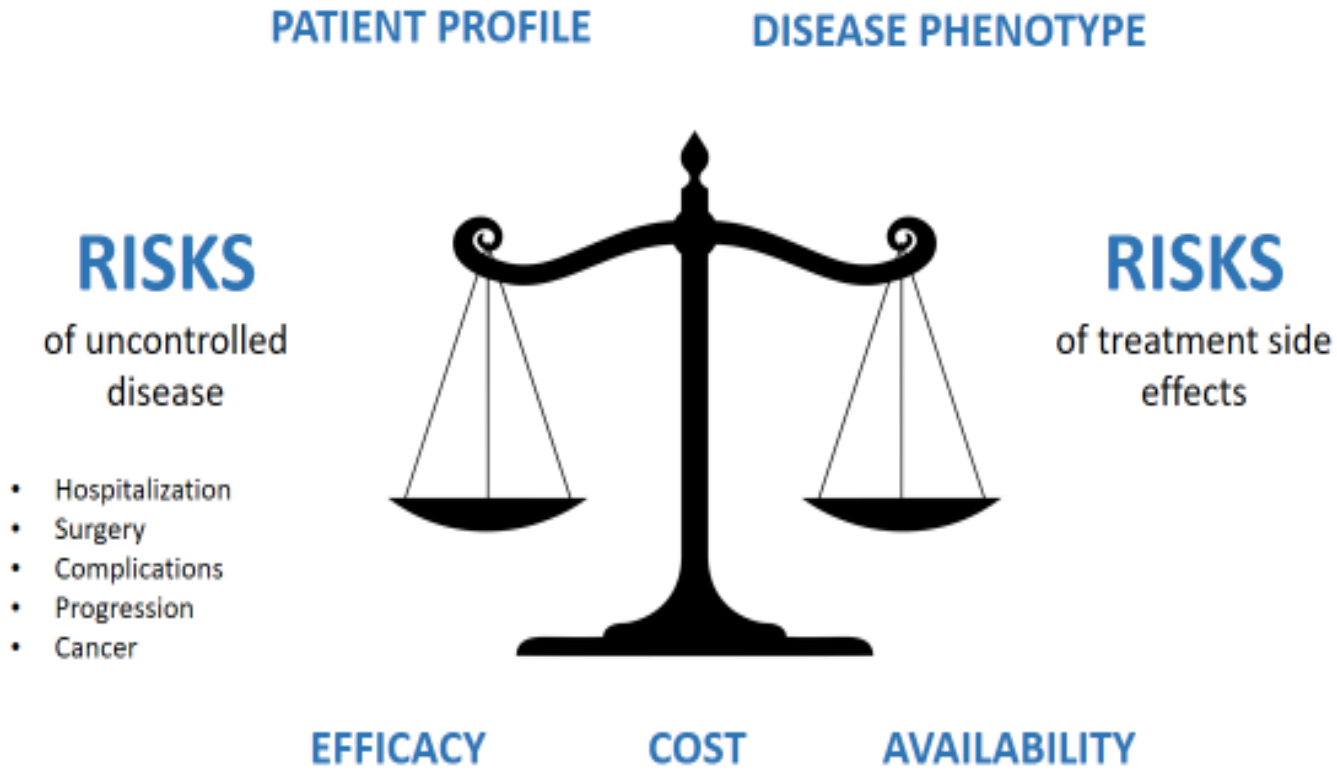
University of KwaZulu- Natal

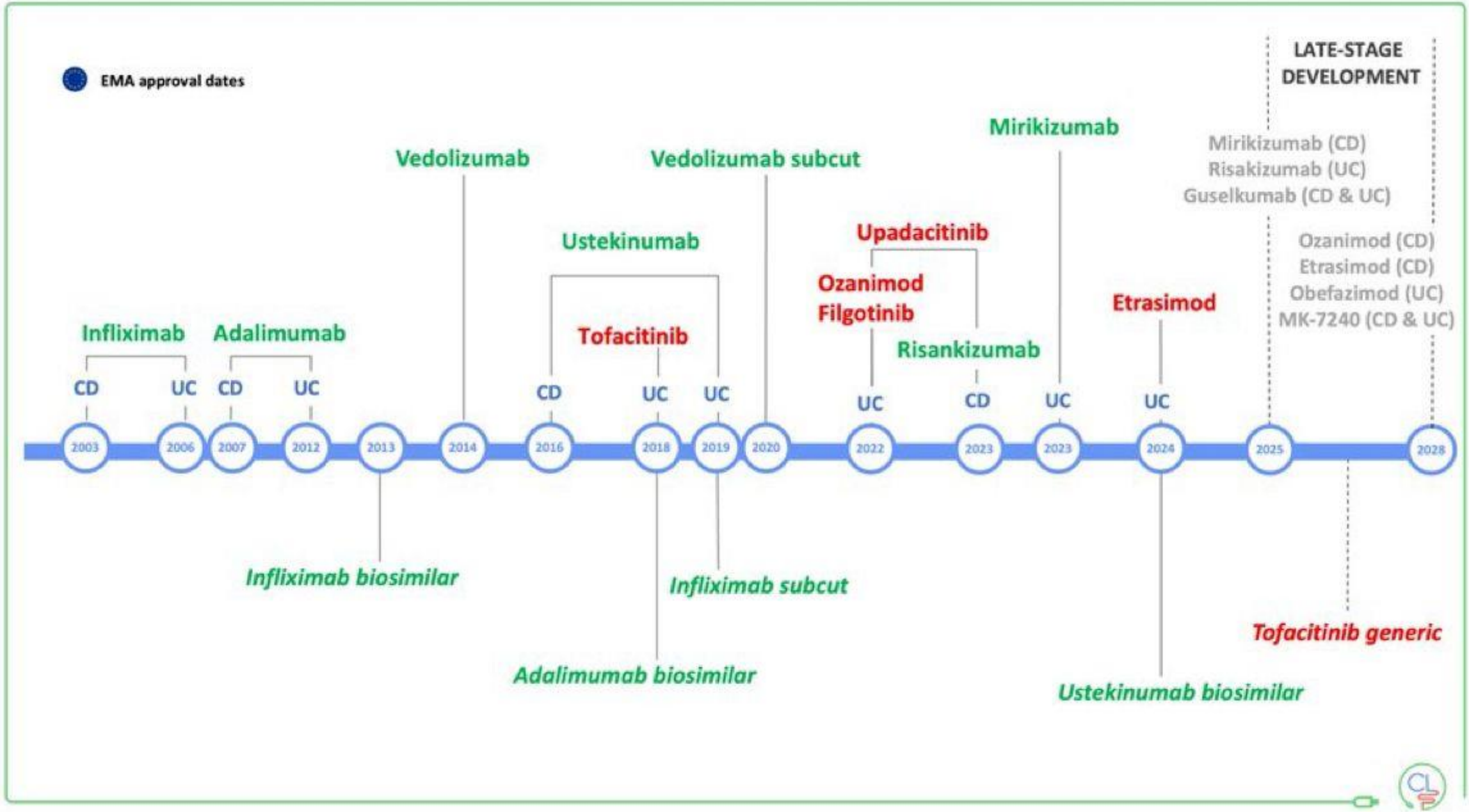
Supervisor: Prof Gill Watermeyer

Monday, 27 November 2023

Introduction

- There is currently no cure for IBD
- Control the inflammatory process
- Conventional treatments have a long history with proven efficacy
- However patients fail to respond, loose response or are intolerant
- Diverse treatment options have emerged- biologics/small molecules





https://twitter.com/charlie_lees

The ‘MABs’

TNF agonists

Infliximab (IVI)

Adalumimab (SC)

Certolizumab (SC)

Golimumab(SC)

Anti Integrins

Vedolizimab (IVI)

Anti interleukins

Ustekinumab(IVI/SC)

Rizankizumab(IVI)

Mirikizumab (IVI)

The ‘NIBs’

JAK Inhibitors

Tofacitinib (oral)

Upadacitinib (oral)

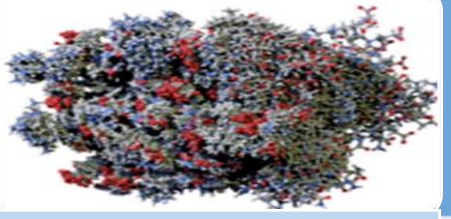
Filgotinib (oral)

The ‘MODs’

(S1P) receptor – modulators

Ozanimod(oral)

Etrasimod (oral)

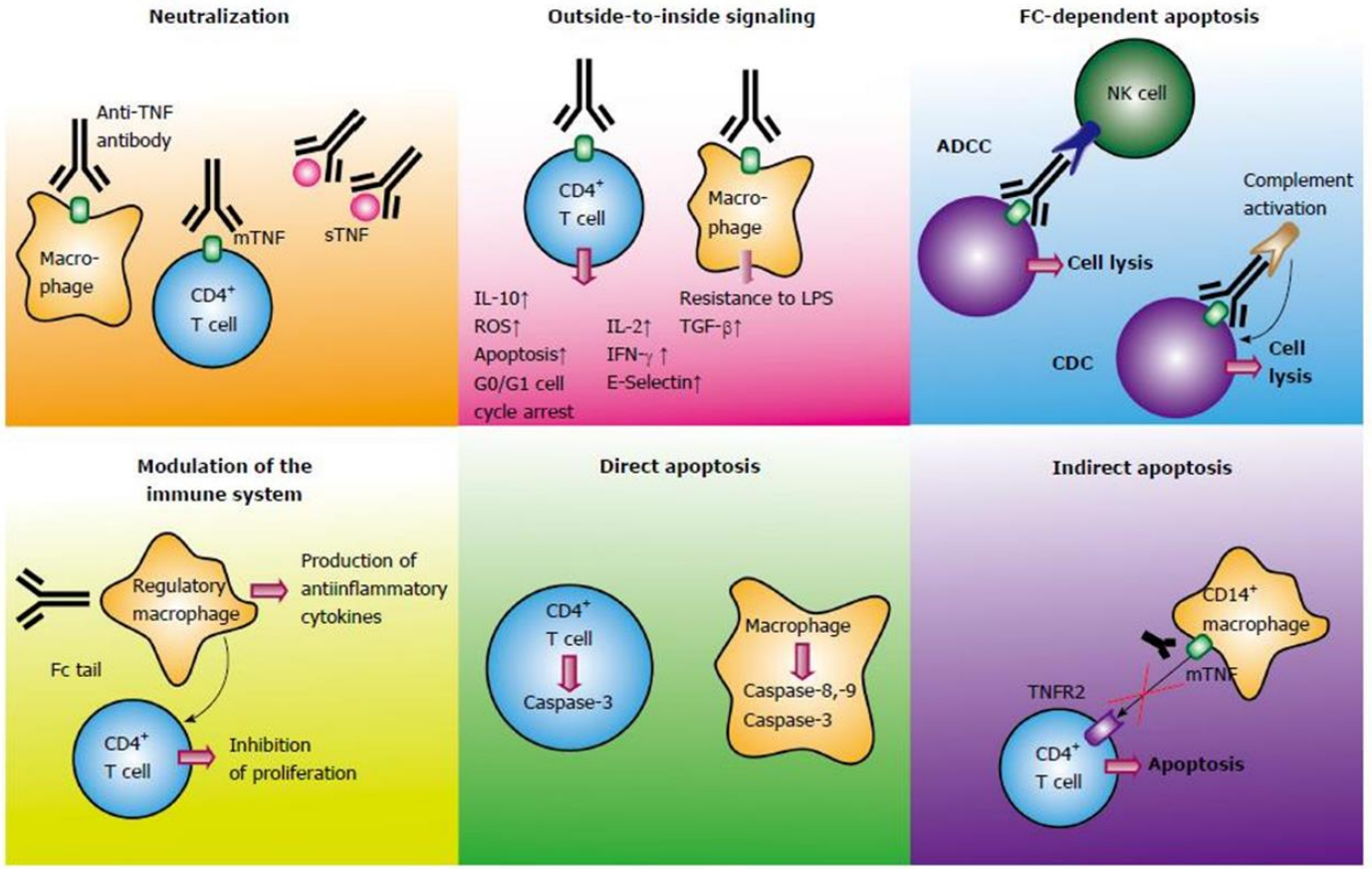
BIOLOGICS	SMALL MOLECULES
	
Large (mixture)	Small (single molecule)
Complex heterogeneous structure	Simple well defined structure
Produced in a living cell structure	Produced by chemical synthesis
Immunogenic	Non-immunogenic
Parenteral administration	Oral administration
Long half life	Short half life

The ‘MABs’

TNFα Agonists - Mechanism of Action

- TNF α plays pivotal role in the inflammatory cascade
- Made intracellulary by activated macrophages
- TNFα and TNF β bind to TNF receptors Ⅰ and Ⅱ - present on all cell types
- Activates several signaling pathways

TNF α agonists- multiple sites of action



Billmeier U et al. World J Gastroenterol 2016; 22(42): 9300-9313

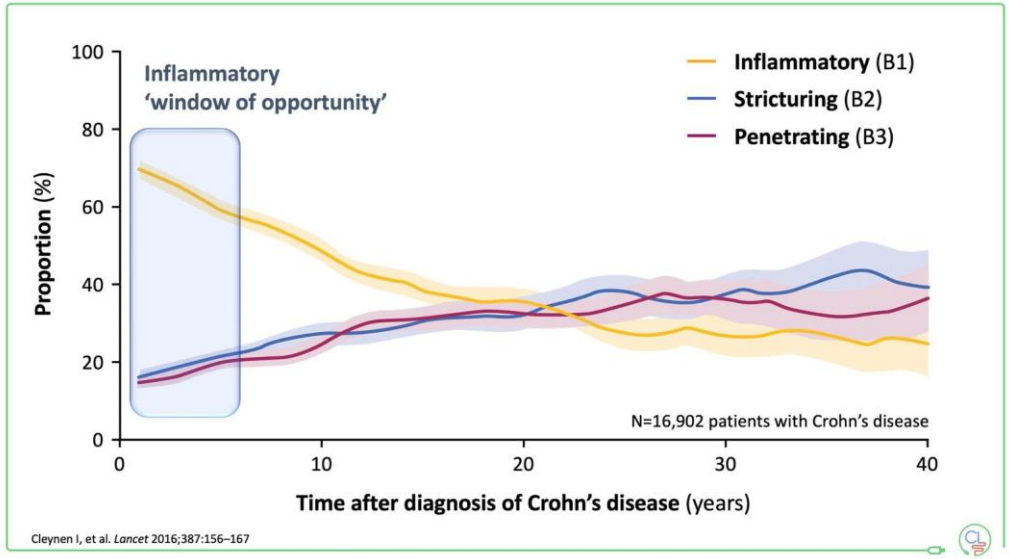
TNFα Agonists- Currently Approved

Type of antibody		Suffix	Anti-TNF α	Approved in	Half life	Standard dose
	Murine	-omab				
	Human	-umab	Adalumimab (SC)	CD,UC	10-13 days	Induce-160mg D1/80mg D15 Maintain- 40mg q2 weeks
			Golimumab(SC)	UC	7-20 days	Induce-200mg D1/100mg D15 Maintain-100mg q4 weeks
	Chimeric	-ximab	Infliximab (IVI)	CD,UC	8-10 days	5mg/kg day Induce 0,2,6 weeks Maintain- q8 weeks
	Humanized	-zumab	Certolizumab (SC)	CD	11-14 days	Induce- 400mg SC D1/D15/D26 Maintain- 400mg q4 weeks

TNF α Agonists- Efficacy in CD

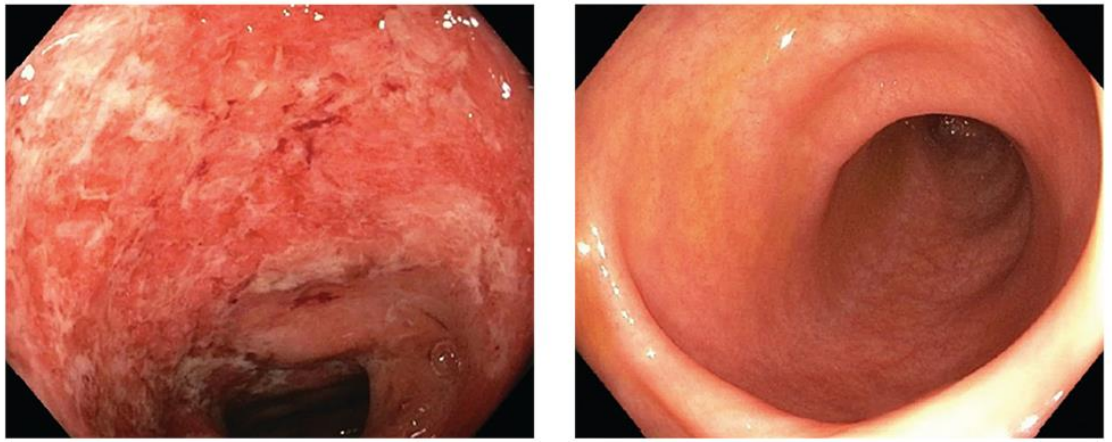
- Indications
  - Refractory luminal CD-IFX/ADA
  - Steroid dependent CD-IFX/ADA
  - Refractory fistulising CD- IFX
  - Refractory extraintestinal manifestations
    - Arthritis/arthralgia
    - Pyoderma gangrenosum/ erythema nodosum
    - Chronic uveitis

- Early biologic use
  - Patients with high risk phenotype
  - Concept of a “therapeutic window of opportunity” in early CD
  - “Step down” approach



TNFα Agonists- Efficacy in UC

- Refractory moderate to severely active UC
  - ACT 1&2- Infliximab
  - ULTRA 1&2-Adalumimab
- Should be instituted early
  - Especially if high risk for colectomy
- Rescue therapy in ASUC- IFX

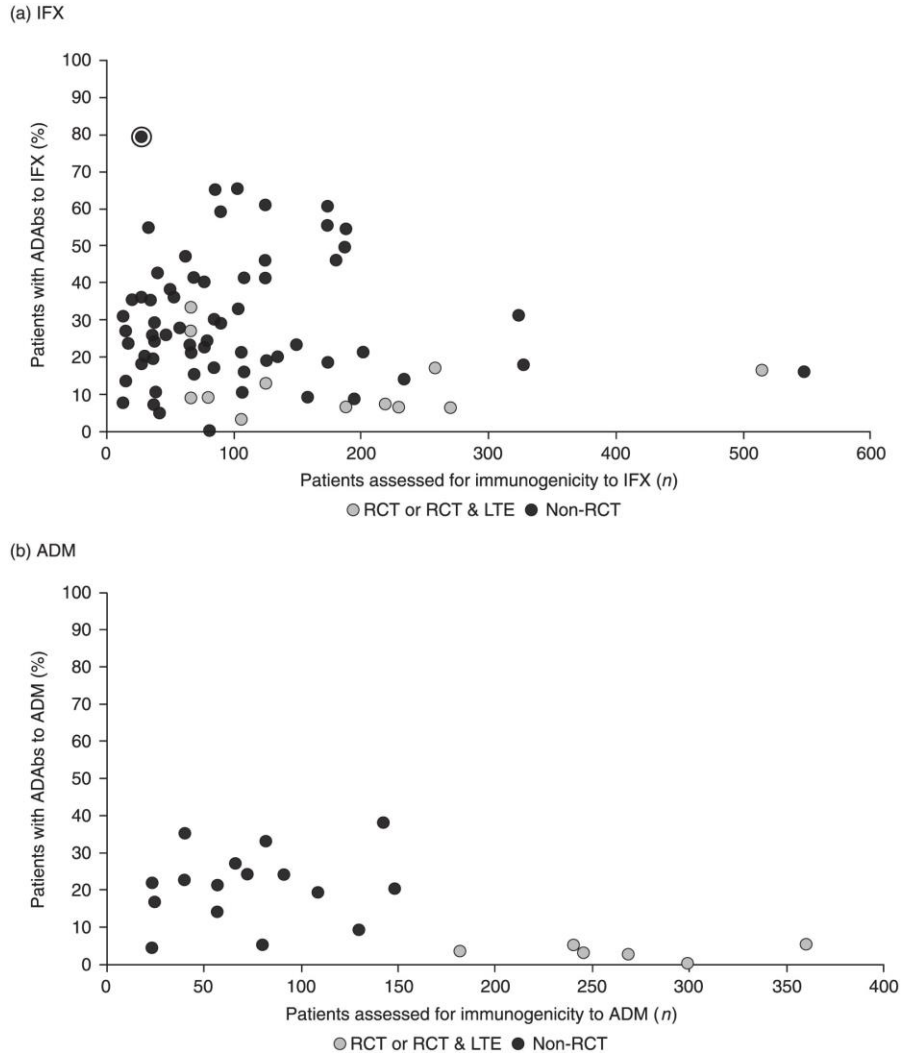


Figures 2a and b. a (left). Acute severe ulcerative colitis prior to anti-TNF therapy. b (right). Endoscopic remission during anti-TNF therapy.
Abbreviation: TNF = tumour necrosis factor.

Tambakis G et al.Medicine Today 2023; 24(3): 14-20.

TNFα agonists and Immunogenicity

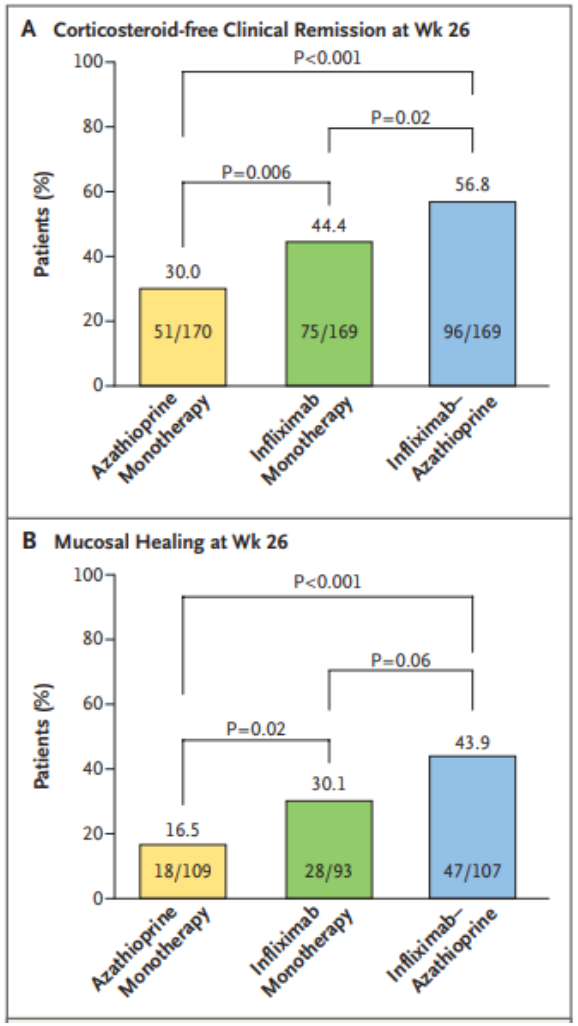
- Immunogenicity leads to a loss of response to biologic therapies
- Biologic agents trigger the formation of anti-drug antibodies (ADAs)
- Humanized MABs produce fewer ADAs than the chimeric MABs
- Vermeire et al-Systematic Review
    - IFX- 74 studies- ADAs 0% to 65.3%
    - ADA- 23 studies- ADAs 0.3% to 38%



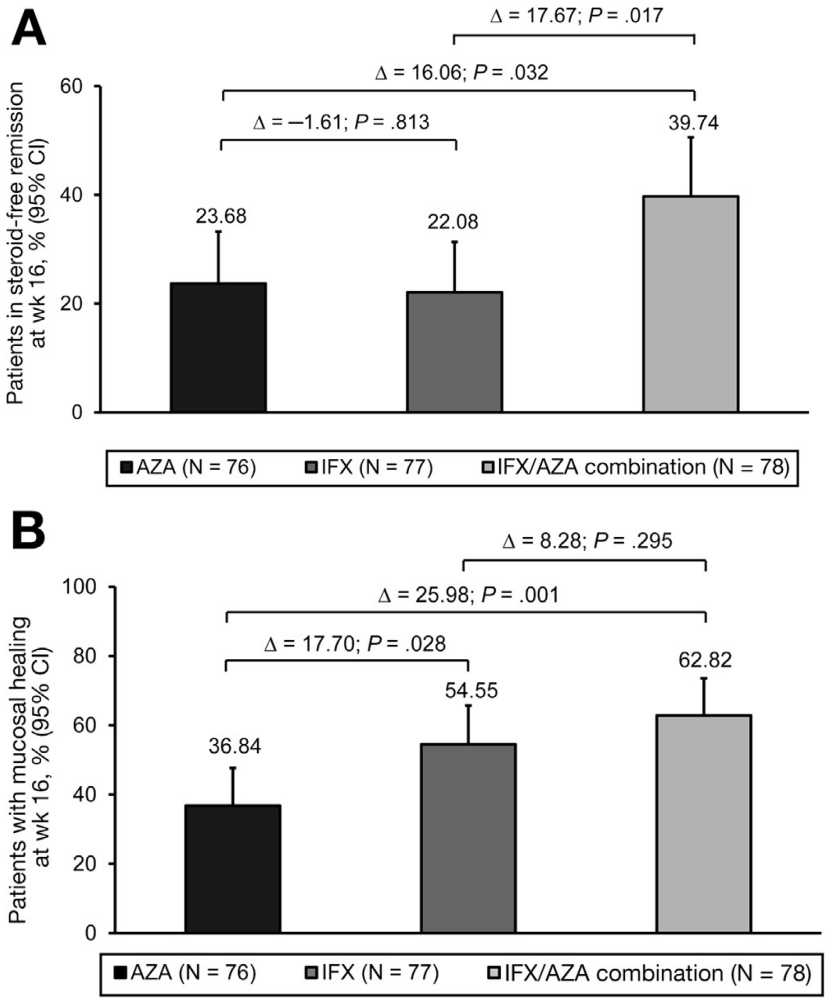
Vermeire S et al. Therapeutic Advances in Gastroenterology. Volume 11, January-December 2018

Combination Therapy-TNFα agonists and AZA

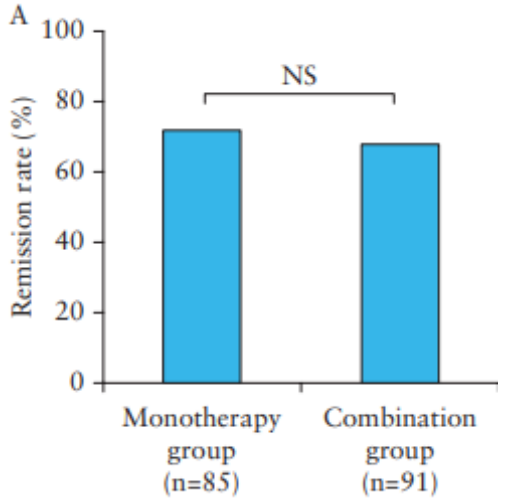
SONIC TRIAL- IFX in CD

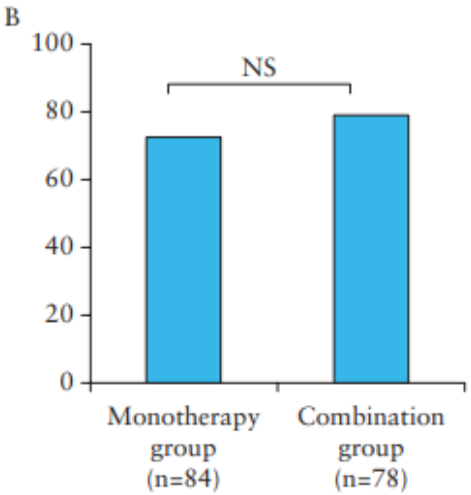


SUCCESS TRIAL- IFX in UC

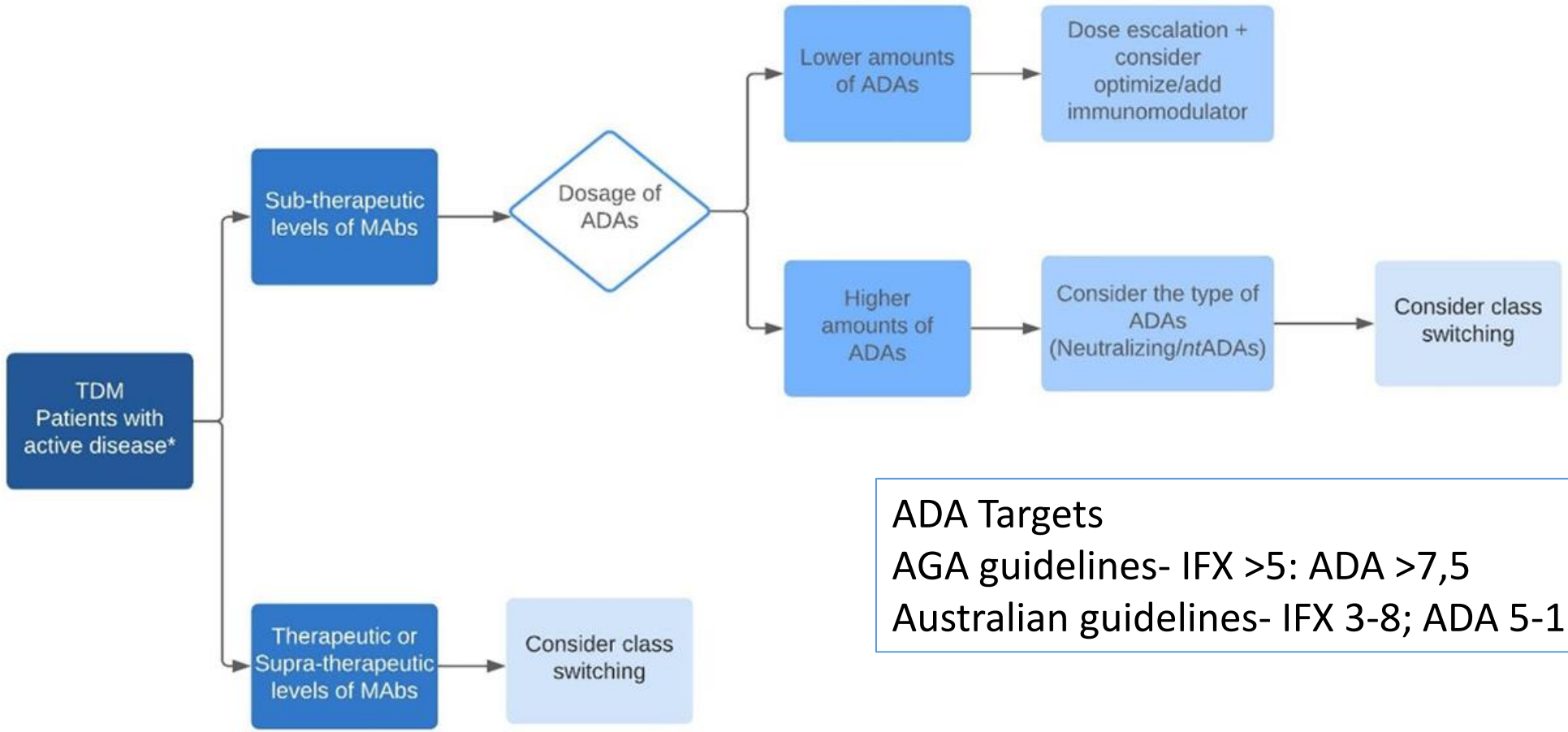


DIAMOND TRIAL- ADA in CD





TNFα Agonists- Therapeutic Drug Monitoring



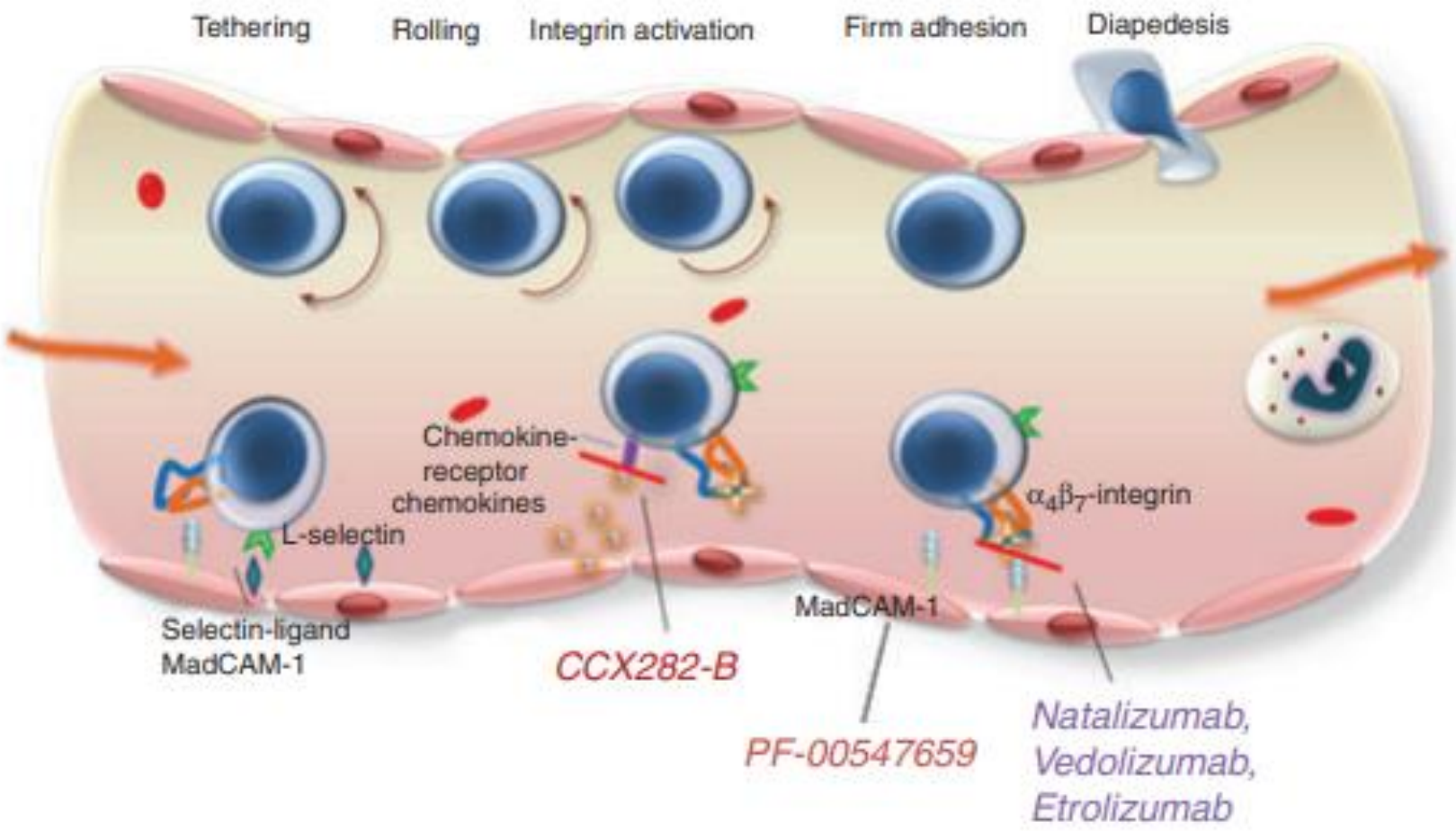
ADA Targets
AGA guidelines- IFX >5: ADA >7,5
Australian guidelines- IFX 3-8; ADA 5-12

Genaro L M. Et al. Am J Transl Res 2021;13(12):13916-13930

TNF α agonists- Safety

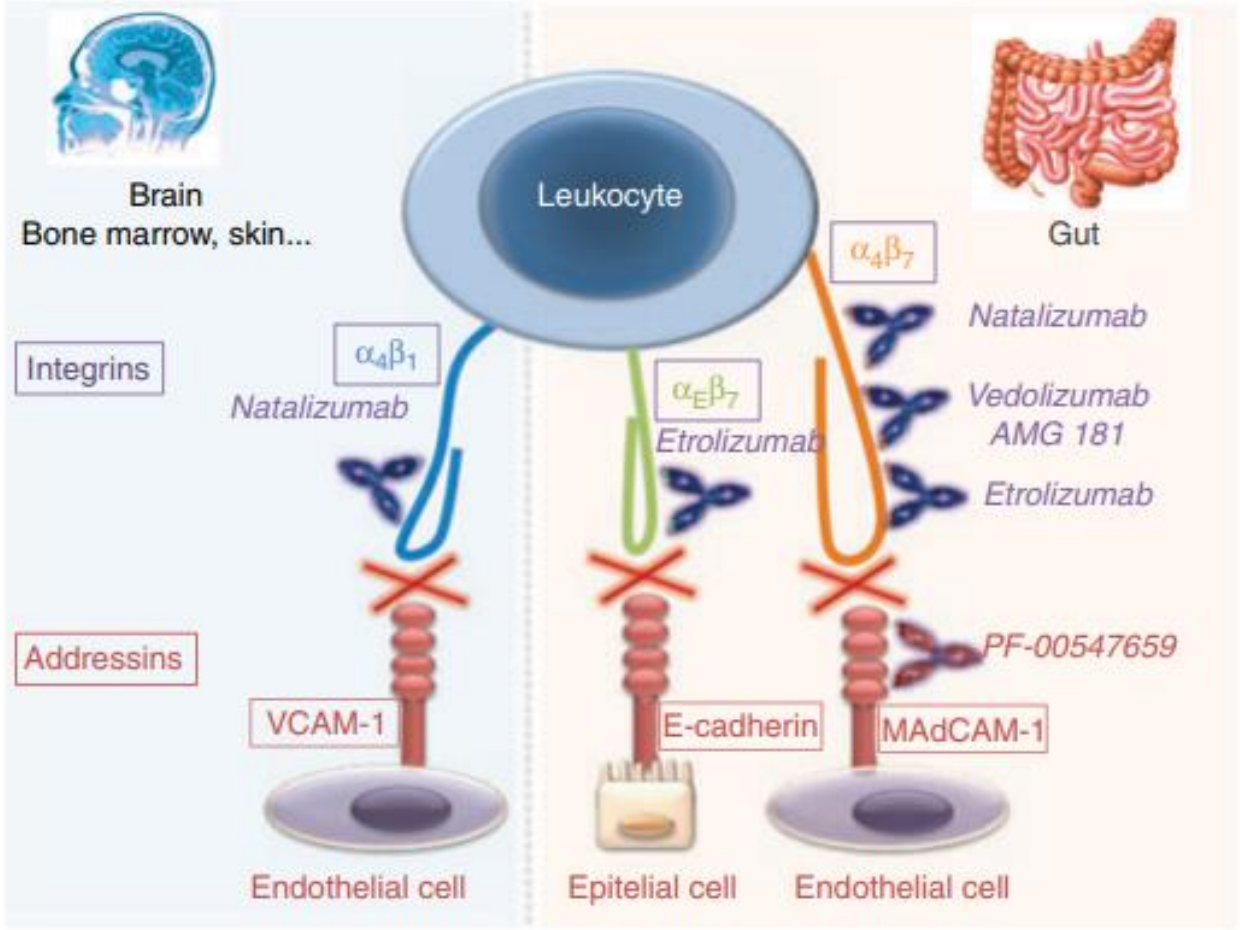
- Increased incidence of infections
  - Bacterial/fungal/viral
  - Reactivation latent TB
  - Hepatitis B reactivation
- Malignancies
  - Non melanoma skin cancer- RA
  - Lymphoma- IBD
  - Lung head and neck if concurrent smoking
- Demyelinating syndromes
  - Reactivation or new onset MS
  - GBS
  - Optic neuritis
- Infusion/injection reactions/ hypersensitivity
  - Minor itching and redness around the site
  - Headache ,dizziness, nausea, hypotension
- Hepatotoxicity
  - Mild elevation in enzymes
  - Fulminant liver failure
- Haemological disorders
  - Neutropenia, leucopenia, anaemia, lymphadenopathy
  - Rare agranulocytosis
- Worsening congestive cardiac failure

Anti Integrins- Mechanism of action



Lobaton T et al. Aliment Pharmacol Ther 2014; 39: 579-594

Anti Integrins- Currently approved



Natalizimab

- Recombinant humanized MAB
- First class anti integrin
- Directed against both α4 β1/α4 β7
- Approved CD/multiple sclerosis
- PML concerns
- no UC trials

Vedolizimab

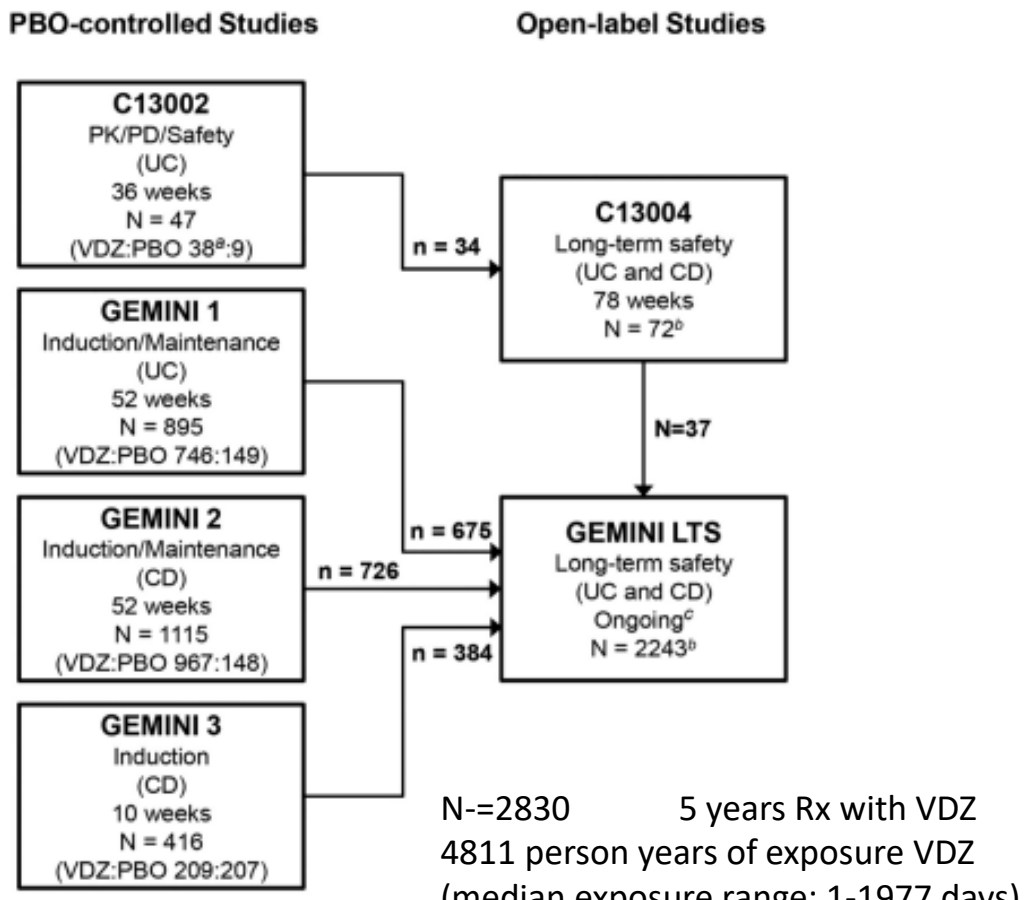
- Humanised MAB
- Specifically targets α4 β7- GI tract/biliary system
- Approved in UC/CD (gut specific)
- lower systemic immunosuppression, lower risk of associated AE's- infection and malignancy

Lobaton T et al. Aliment Pharmacol Ther 2014; 39: 579-594

Vedolizumab- Efficacy in UC and CD

- **Indications**
  - Induction and maintenance in patients with moderate to severely active UC and CD
  - Efficacy data from GEMINI series
    - GEMINI 1- UC
    - GEMINI 2&3- CD
  - Vedolizumab as first line biologic in UC
  - Earnest trial -VDZ more effective than placebo in chronic pouchitis
- **No Role**
  - ASUC
  - Fistulising CD
  - Extra intestinal disease (gut specific)
    - Vedolizumab induced De Novo EIM

Vedolizimab- Safety- (Integrated study)

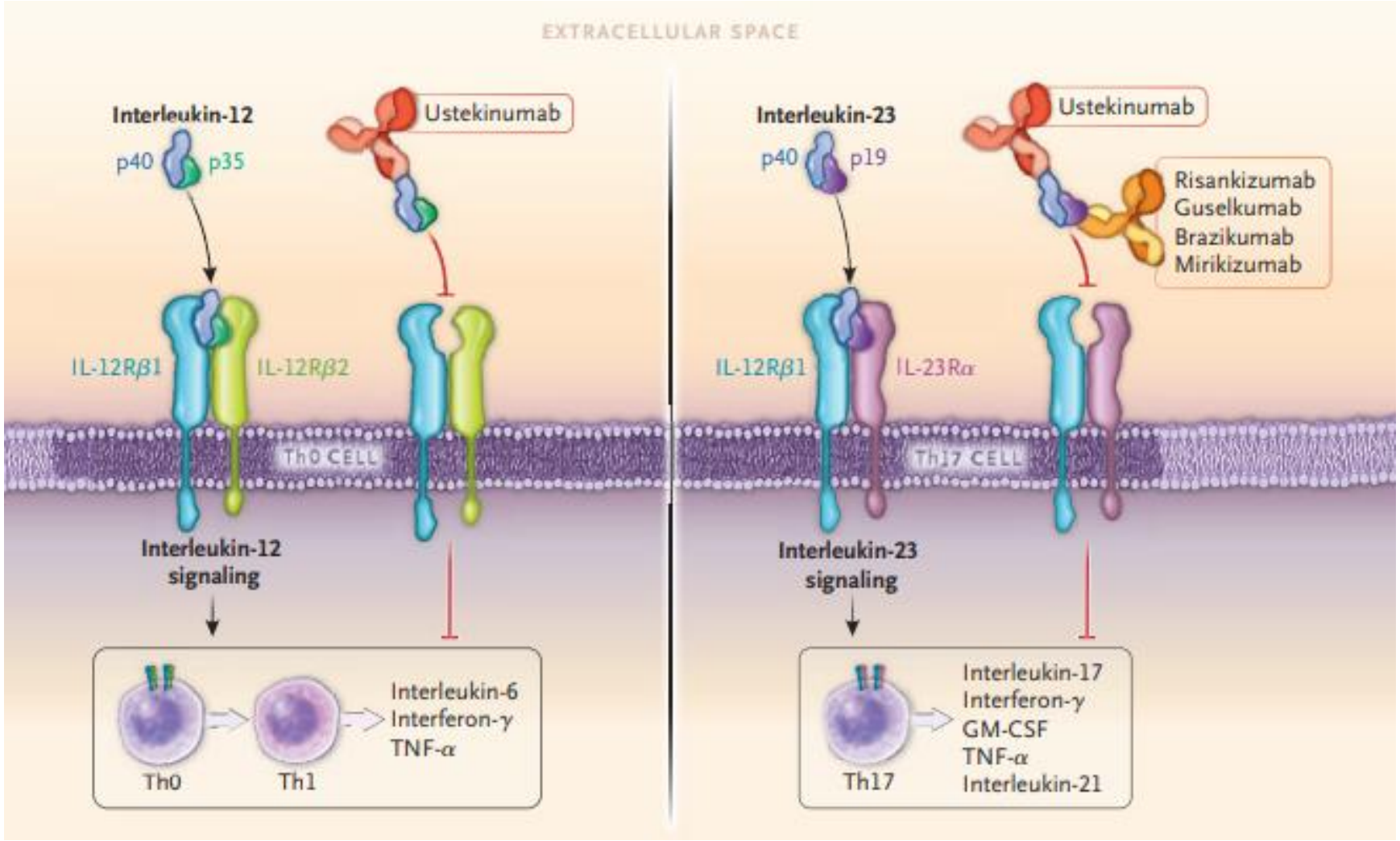


N-=2830 5 years Rx with VDZ
4811 person years of exposure VDZ
(median exposure range: 1-1977 days)

- No increased risk of any infection or serious infection in VDZ exposed
- Serious clostridial infections, sepsis and TB reported infrequently (<0.6%)
- No cases of PML observed
- Infusion related reactions <5%
- 18 (<1%) VDZ exposed patients developed malignancy
- 23 hepatobiliary events in VDZ-treated patients
- Immunogenicity rate low, did not appear to increase over time

Colombel J-F, et al. Gut2017;66:839-851

Anti-Interleukins- Mechanism of action



Baumgart D C et al. N Engl J Med 2021;385:1302-15.

Ustekinumab (anti IL12/23) Efficacy in CD & UC

Crohns disease

- Indicated in moderate to severe CD
- Phase 3 UNITI program- efficacy
- Real world data- remission maintained in TNF experienced patients

- **Ulcerative colitis**
  - Indicated in moderate to severe UC
  - Phase 3 UNIFI program- efficacy
  - Efficacy> Biologic naïve
  - The UNIFI trial- histo-endoscopic mucosal healing as an endpoint

- **Immunogenicity**
  - The Incidence of antibodies is low
  - Value of combination therapy unclear

- **Extraintestinal manifestations**
  - Co morbid psoriasis
  - TNF induced alopecia
  - Not efficacious in Ankylosing spondylitis

Selective Anti IL23- Efficacy in CD and UC

- IL-23 is more potent driver of inflammation than IL-12

- Rizankizumab approved in CD (ADVANCED, MOTIVATE and FORTIFY)
- Mirikizumab approved in UC (LUCENT 1, LUCENT 2)

- Head-to-head psoriasis trials showed superior efficacy of IL-23 to Ustekinumab
- Selective IL-23- Promising but additional studies are warranted

Anti-Interleukins- Ustekinumab Safety

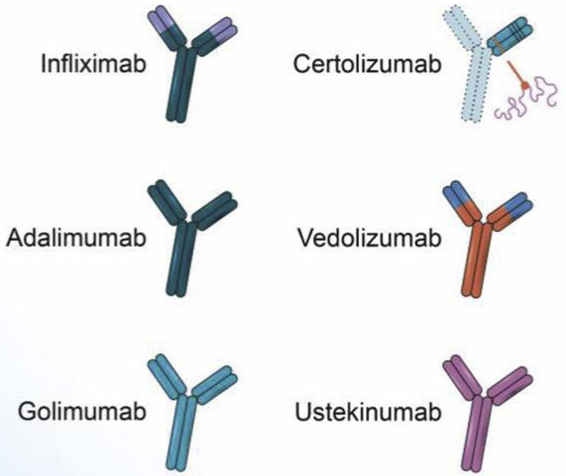
- The safety profile of Ustekinumab is excellent
- The Psoriasis Longitudinal Assessment and Registry (PSOLAR) registry
  - N-12000
  - No increased risk of malignancy, MACE, serious infection, or mortality
- No head-to-head trials comparing safety of anti IL12/23 and anti TNFs
  - Network meta-analysis
  - lower rate of serious infections and tuberculosis has been observed with Ustekinumab compared to anti TNF agents

Biologics- Precautions and Monitoring

Biologics and safety in IBD pregnancies

Study group

Women on biologics:

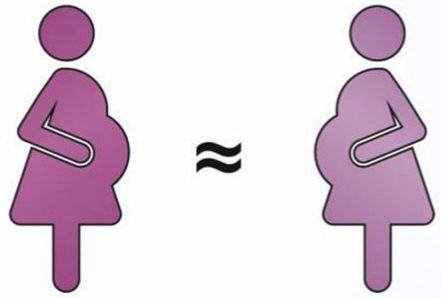


Studies included

Outcome	Studies	Participants	Pooled prevalence	
			Biologics	General population
Early pregnancy loss	37	4410	8 %	14 %
Preterm birth	32	3466	9 %	11 %
Stillbirth	25	4143	0 %	2 %
Low birth weight	23	1943	8 %	6 %
Congenital malformation	44	5176	1 %	3 %

Findings

Adverse pregnancy outcomes:



IBD women on biologics (including 3rd trimester)

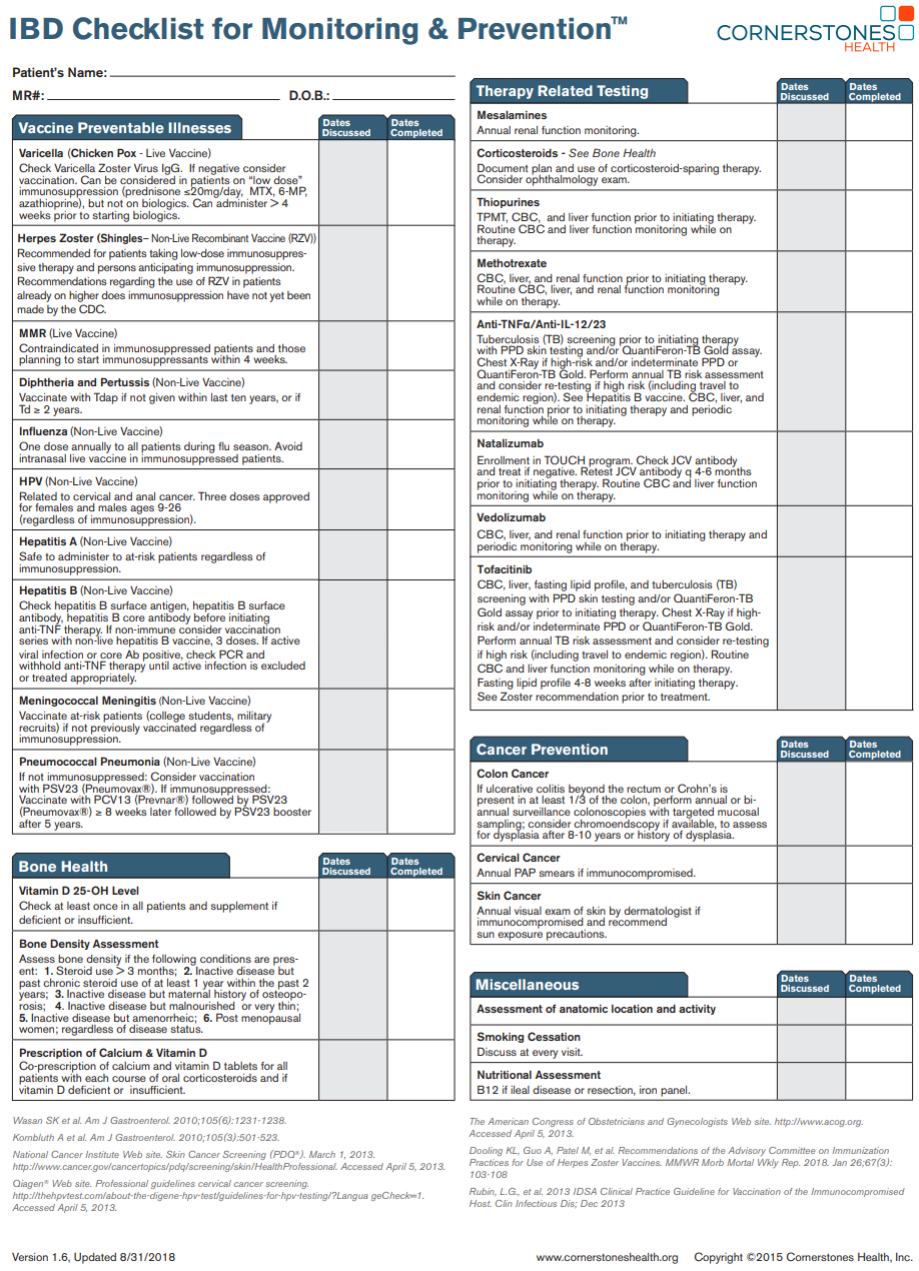
General population

Clinical Gastroenterology and Hepatology

Nielsen O H et al. Clinical Gastroenterology and Hepatology.2022;20:74-87

Biologics Precautions and Monitoring

- Baseline biochemical/clinical screening
- Vaccinations
- Non Pharmacological



IBD Checklist for Monitoring & Prevention™

CORNERSTONES HEALTH

Patient's Name: _____

MR#: _____ D.O.B.: _____

Vaccine Preventable Illnesses

	Dates Discussed	Dates Completed
Varicella (Chicken Pox - Live Vaccine) Check Varicella Zoster Virus IgG. If negative consider vaccination. Can be considered in patients on "low dose" immunosuppression (prednisone ≤20mg/day, MTX, 6-MP, azathioprine), but not on biologics. Can administer > 4 weeks prior to starting biologics.		
Herpes Zoster (Shingles– Non-Live Recombinant Vaccine (RZV)) Recommended for patients taking low-dose immunosuppressive therapy and persons anticipating immunosuppression. Recommendations regarding the use of RZV in patients already on higher does immunosuppression have not yet been made by the CDC.		
MMR (Live Vaccine) Contraindicated in immunosuppressed patients and those planning to start immunosuppressants within 4 weeks.		
Diphtheria and Pertussis (Non-Live Vaccine) Vaccinate with Tdap if not given within last ten years, or if Td ≥ 2 years.		
Influenza (Non-Live Vaccine) One dose annually to all patients during flu season. Avoid intranasal live vaccine in immunosuppressed patients.		
HPV (Non-Live Vaccine) Related to cervical and anal cancer. Three doses approved for females and males ages 9-26 (regardless of immunosuppression).		
Hepatitis A (Non-Live Vaccine) Safe to administer to at-risk patients regardless of immunosuppression.		
Hepatitis B (Non-Live Vaccine) Check hepatitis B surface antigen, hepatitis B surface antibody, hepatitis B core antibody before initiating anti-TNF therapy. If non-immune consider vaccination series with non-live hepatitis B vaccine, 3 doses. If active viral infection or core Ab positive, check PCR and withhold anti-TNF therapy until active infection is excluded or treated appropriately.		
Meningococcal Meningitis (Non-Live Vaccine) Vaccinate at-risk patients (college students, military recruits) if not previously vaccinated regardless of immunosuppression.		
Pneumococcal Pneumonia (Non-Live Vaccine) If not immunosuppressed: Consider vaccination with PSV23 (Pneumovax®). If immunosuppressed: Vaccinate with PCV13 (Prevnar®) followed by PSV23 (Pneumovax®) ≥ 8 weeks later followed by PSV23 booster after 5 years.		

Bone Health

	Dates Discussed	Dates Completed
Vitamin D 25-OH Level Check at least once in all patients and supplement if deficient or insufficient.		
Bone Density Assessment Assess bone density if the following conditions are present: **1.** Steroid use > 3 months; **2.** Inactive disease but past chronic steroid use of at least 1 year within the past 2 years; **3.** Inactive disease but maternal history of osteoporosis; **4.** Inactive disease but malnourished or very thin; **5.** Inactive disease but amenorrheic; **6.** Post menopausal women; regardless of disease status.		
Prescription of Calcium & Vitamin D Co-prescription of calcium and vitamin D tablets for all patients with each course of oral corticosteroids and if vitamin D deficient or insufficient.		

Therapy Related Testing

	Dates Discussed	Dates Completed
Mesalamines Annual renal function monitoring.		
Corticosteroids - *See Bone Health* Document plan and use of corticosteroid-sparing therapy. Consider ophthalmology exam.		
Thiopurines TPMT, CBC, and liver function prior to initiating therapy. Routine CBC and liver function monitoring while on therapy.		
Methotrexate CBC, liver, and renal function prior to initiating therapy. Routine CBC, liver, and renal function monitoring while on therapy.		
Anti-TNFα/Anti-IL-12/23 Tuberculosis (TB) screening prior to initiating therapy with PPD skin testing and/or QuantiFeron-TB Gold assay. Chest X-Ray if high-risk and/or indeterminate PPD or QuantiFeron-TB Gold. Perform annual TB risk assessment and consider re-testing if high risk (including travel to endemic region). See Hepatitis B vaccine. CBC, liver, and renal function prior to initiating therapy and periodic monitoring while on therapy.		
Natalizumab Enrollment in TOUCH program. Check JCV antibody and treat if negative. Retest JCV antibody q 4-6 months prior to initiating therapy. Routine CBC and liver function monitoring while on therapy.		
Vedolizumab CBC, liver, and renal function prior to initiating therapy and periodic monitoring while on therapy.		
Tofacitinib CBC, liver, fasting lipid profile, and tuberculosis (TB) screening with PPD skin testing and/or QuantiFeron-TB Gold assay prior to initiating therapy. Chest X-Ray if high-risk and/or indeterminate PPD or QuantiFeron-TB Gold. Perform annual TB risk assessment and consider re-testing if high risk (including travel to endemic region). Routine CBC and liver function monitoring while on therapy. Fasting lipid profile 4-8 weeks after initiating therapy. See Zoster recommendation prior to treatment.		

Cancer Prevention

	Dates Discussed	Dates Completed
Colon Cancer If ulcerative colitis beyond the rectum or Crohn's is present in at least 1/3 of the colon, perform annual or bi-annual surveillance colonoscopies with targeted mucosal sampling; consider chromoendscopy if available, to assess for dysplasia after 8-10 years or history of dysplasia.		
Cervical Cancer Annual PAP smears if immunocompromised.		
Skin Cancer Annual visual exam of skin by dermatologist if immunocompromised and recommend sun exposure precautions.		

Miscellaneous

	Dates Discussed	Dates Completed
Assessment of anatomic location and activity		
Smoking Cessation Discuss at every visit.		
Nutritional Assessment B12 if ileal disease or resection, iron panel.		

Wasan SK et al. Am J Gastroenterol. 2010;105(6):1231-1238.

Kornbluth A et al. Am J Gastroenterol. 2010;105(3):501-523.

National Cancer Institute Web site. Skin Cancer Screening (PDQ®). March 1, 2013. http://www.cancer.gov/cancertopics/pdq/screening/skin/HealthProfessional. Accessed April 5, 2013.

Qiagen® Web site. Professional guidelines cervical cancer screening. http://thehpvtest.com/about-the-digene-hpv-test/guidelines-for-hpv-testing/?Langua geCheck=1. Accessed April 5, 2013.

The American Congress of Obstetricians and Gynecologists Web site. http://www.acog.org. Accessed April 5, 2013.

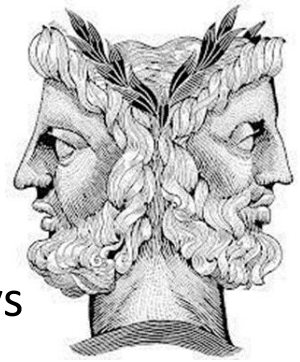
Dooling KL, Guo A, Patel M, et al. Recommendations of the Advisory Committee on Immunization Practices for Use of Herpes Zoster Vaccines. MMWR Morb Mortal Wkly Rep. 2018. Jan 26;67(3): 103-108

Rubin, L.G., et al. 2013 IDSA Clinical Practice Guideline for Vaccination of the Immunocompromised Host. Clin Infectious Dis; Dec 2013

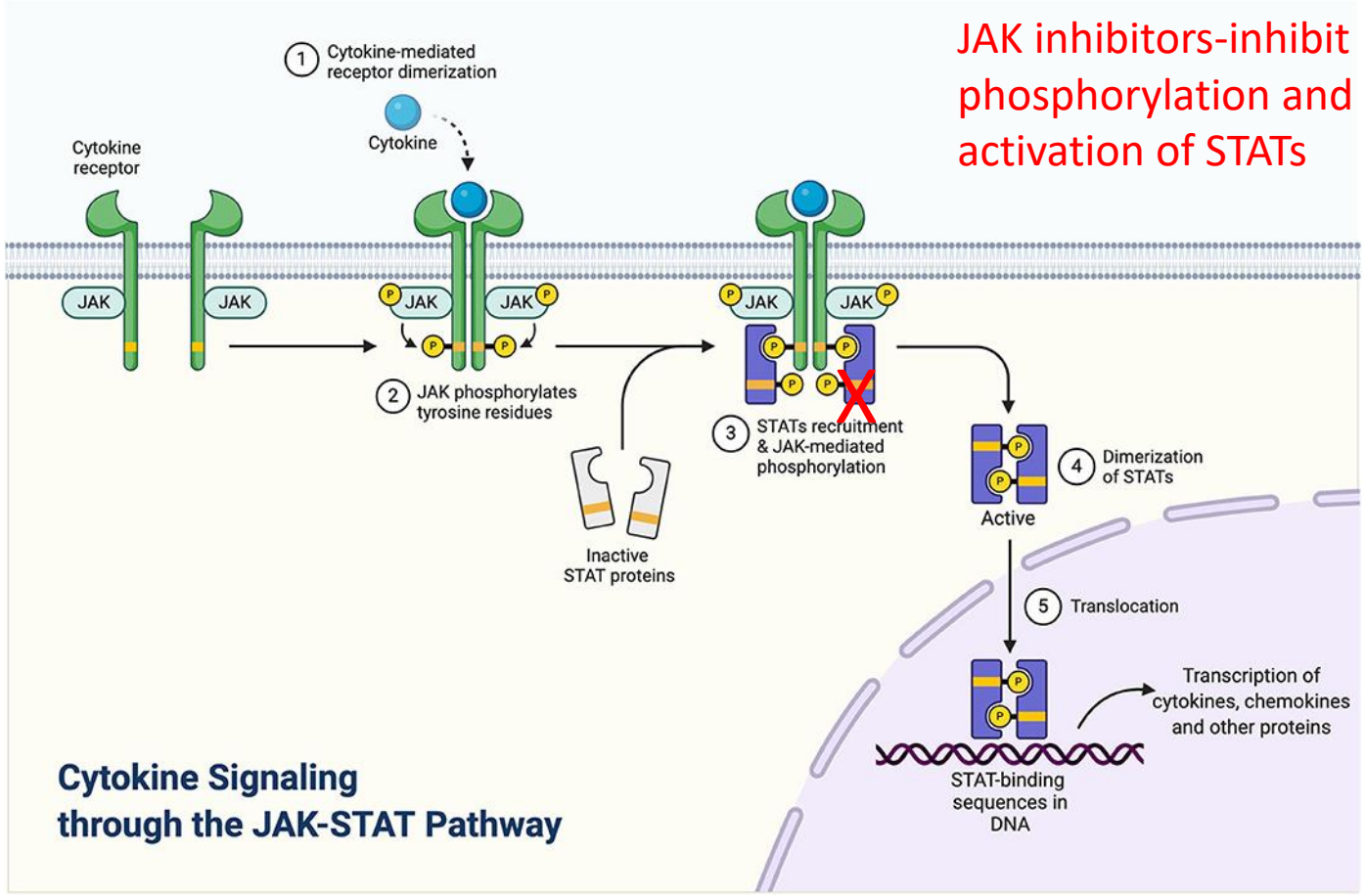
Version 1.6, Updated 8/31/2018

The ‘NIBs’

JAK Inhibitors- Mechanism of action



Janus =Greek God of doorways



1. Cytokines bind to cell surface receptors
2. JAKs are activated by phosphorylation
3. STATs bind to the receptor and are phosphorylated and activated by JAKS
4. Activated STATS then dimerize
5. Translocation to the nucleus where they modulate gene expression and increase pro-inflammatory cytokines

Le et al. Frontiers in Medicine. September 2021,volume 8,article 682547

JAK Inhibitors- Mechanism of action

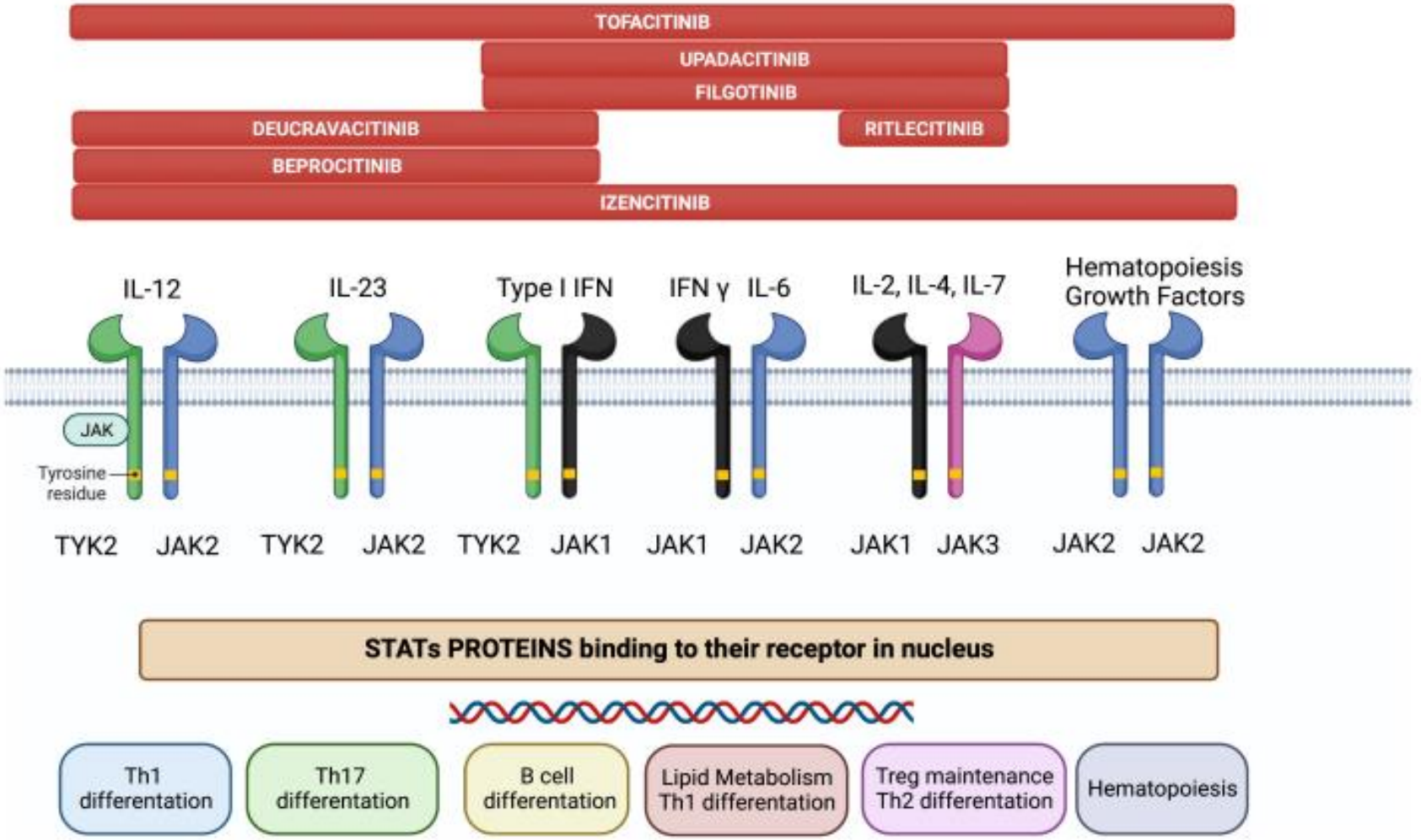


FIGURE 1

Herrera-deGuise et al. Front. Med. 10:1089099.

JAK Inhibitors- Efficacy in UC

- Tofacitinib, Filgotinib and Upadacitinib- approved in UC

- Upadacitinib trials- much more stringent definition of remission and criteria for mucosal healing required both endoscopic and histological remission
  - Induction remission rates between 26%- 34%

- Option second-line therapy in patients with EIM
  - Tofacitinib> placebo in ankylosing spondylitis
  - Tofacitinib successfully treat refractory uveitis, scleritis and pyoderma gangrenosum

JAK Inhibitors work fast

Upadacitinib

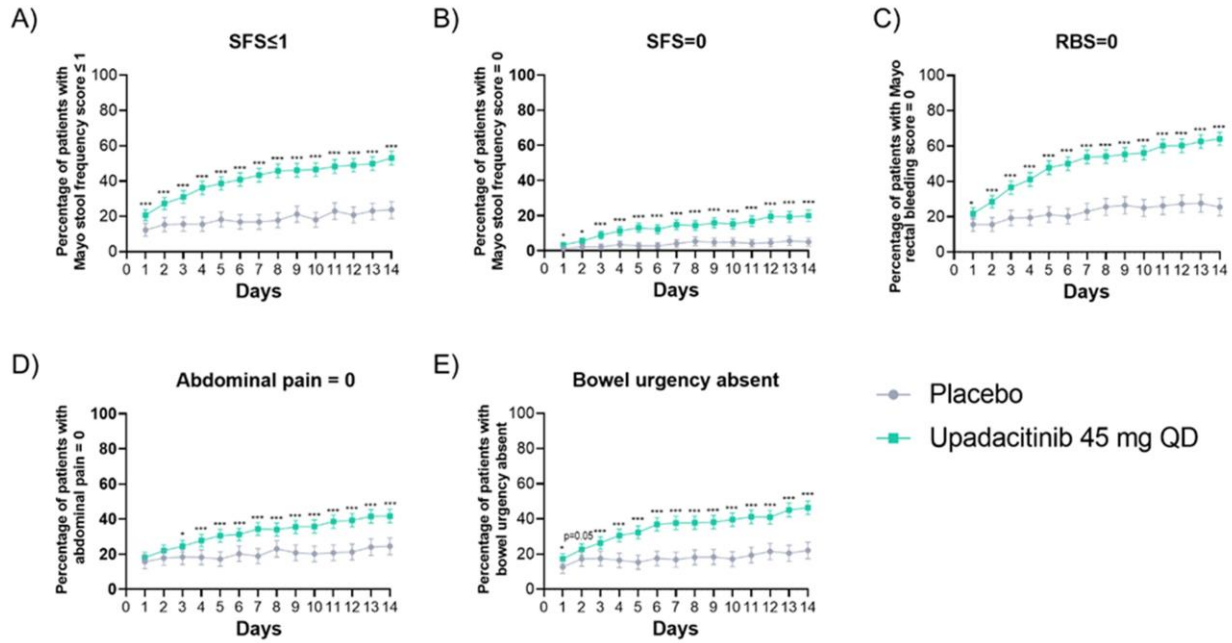
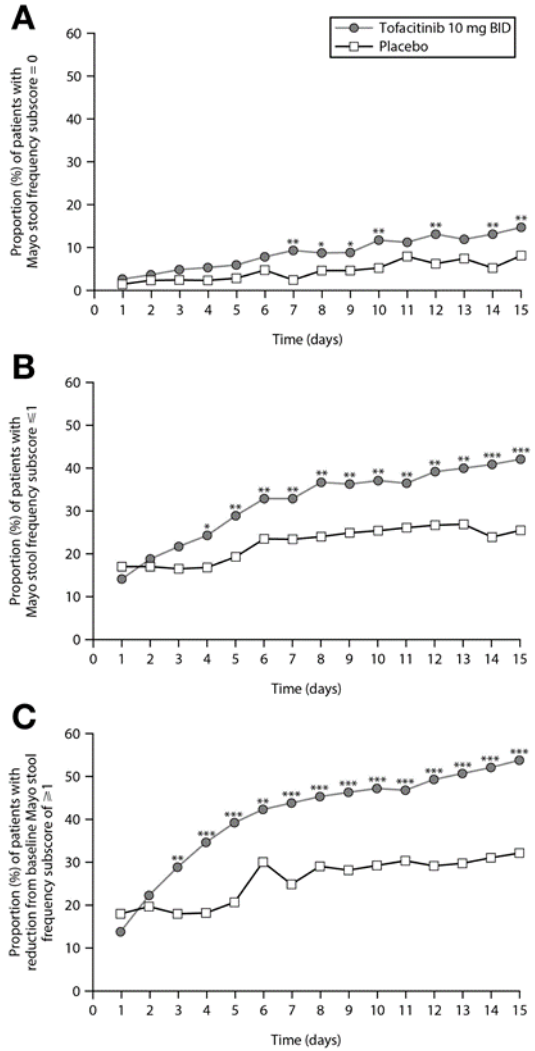


Figure 1. UPA 45 mg QD improves daily abdominal symptoms as early as day 1 of treatment. Percentage of patients with symptomatic improvement in A) SFS≤1, B) SFS=0, C) RBS=0, D) abdominal pain score of 0, and E) Bowel urgency absent for the first 14 days of treatment. Day 0 represents the first day of randomization and first dose of treatment. Patient numbers for all parameters and timepoints were N=303-319 PBO and N=623-647 UPA 45 mg QD. Error bars are ±standard error. *P ≤0.05. **P ≤ 0.01. ***P ≤ 0.001 vs PBO.

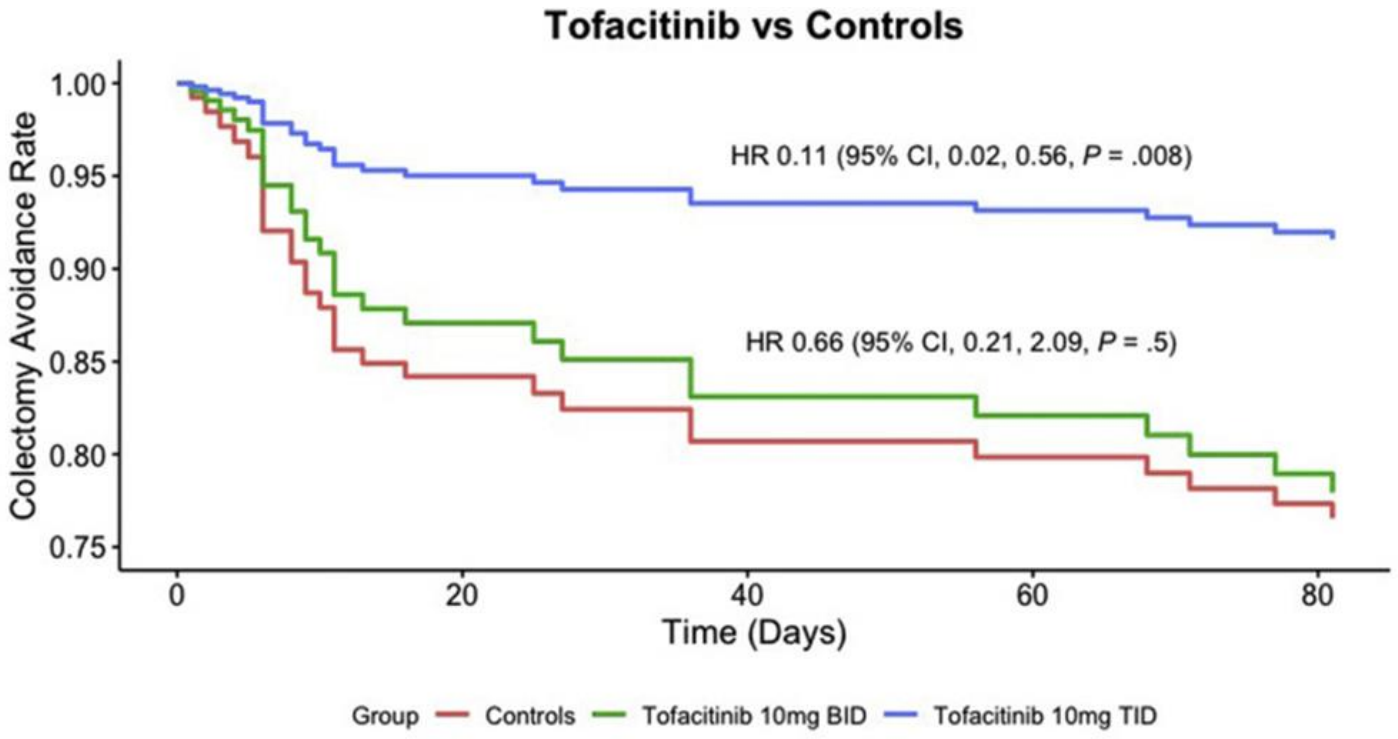
Tofacitinib



1. Loftus E V et al. Clinical Gastroenterology and Hepatology 2023:21. 2347-2358
2. Hanauer S at al.Clinical Gastroenterology and Hepatology 2019:17.139-147

Tofacitinib for Biologic-Experienced Hospitalized Patients With Acute Severe Ulcerative Colitis: A Retrospective Case-Control Study

- 40 biologic-experienced patients with ASUC
- 113 matched controls
- Colectomy rates 8% in the high dose Tofacitinib group



Two ongoing prospective open label studies- TRIUMPH and TOCASU- should provide further evidence

Jeffrey A. Berinstein et al.Clinical Gastroenterology and Hepatology 2021;19:2112-2120

JAK Inhibitors- Efficacy in CD

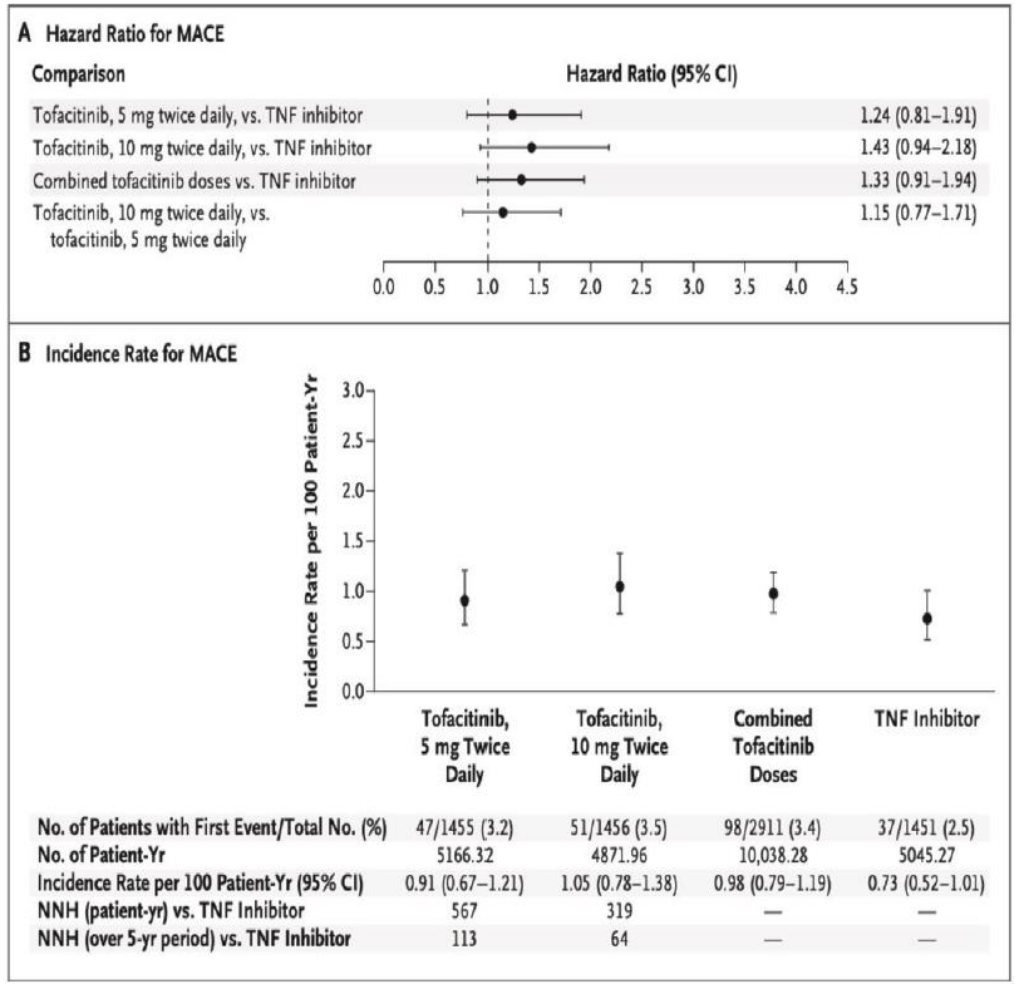
- Tofacitinib testing for CD- stopped after phase II trials
- Filgotinib met efficacy targets in the phase 2 FITZROY study but failed to meet primary targets in the phase 3 DIVERSITY trial
- Only JAK inhibitor approved for use in CD is Upadacitinib

  (U-EXCEL, U- EXCEED,U-ENDURE)
  - 52 Week- clinical remission :15-mg- 37.3% vs 30-mg -47.6% vs placebo- 15.1%
  - Rapid improvement
  - Oral agent in refractory CD

JAK inhibitors- Safety

- Elevated cholesterol
- Infections- herpes zoster
- Thromboembolic event
- Malignancy
- Increased creatinine
- Increased hepatic enzymes
- Increased CK
- Teratogenicity
- Nasopharyngitis

JAK Inhibitors- Safety



ORAL surveillance: open-label, randomized noninferiority and safety end-point trial

- Rheumatoid arthritis (RA)
- > 50 years
- At least one (CV) risk factor at baseline
- Tofacitinib 5 or 10 mg twice daily or TNF Inhibitor
- Higher proportion of MACE and cancer compared with the control group

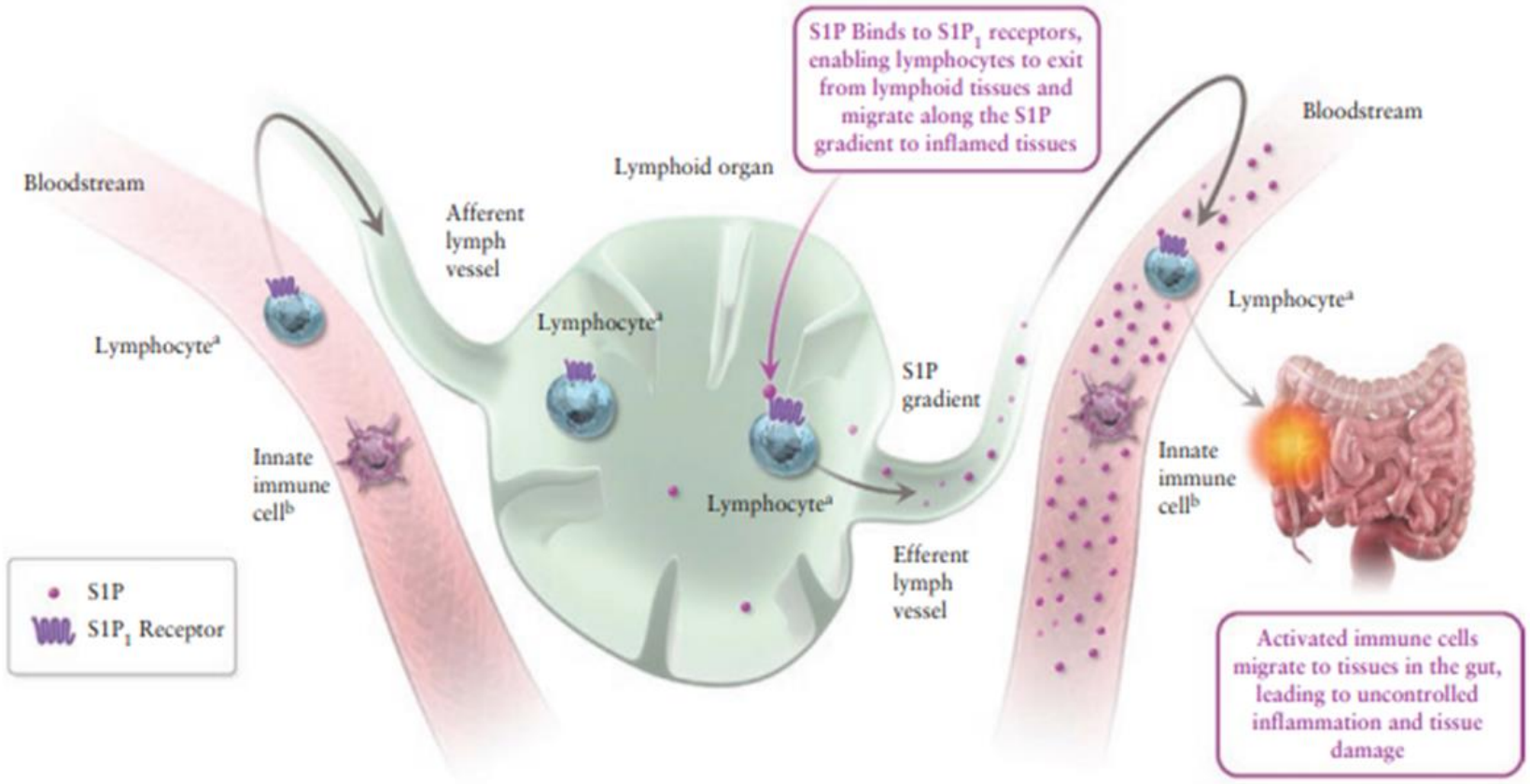
Black Box warning- 7/2020
- Recommendation to give only after anti TNF failure or intolerance
- Give lowest dose during maintenance therapy- 5mg bd
- Stop Tofacitinib if no response after 16 weeks

- IBD and RA
  - Different pathogenesis, epidemiology and risk factors

Ytterberg S et al. N Engl J Med. 2022;386(4):316-326

The ‘MODs’

Sphingosine- 1 phosphate (S1P) receptor- modulators
Ozanimod- Mechanism of action



Ozanimod binds to S1P1 and S1P5 receptors

Functions S1P

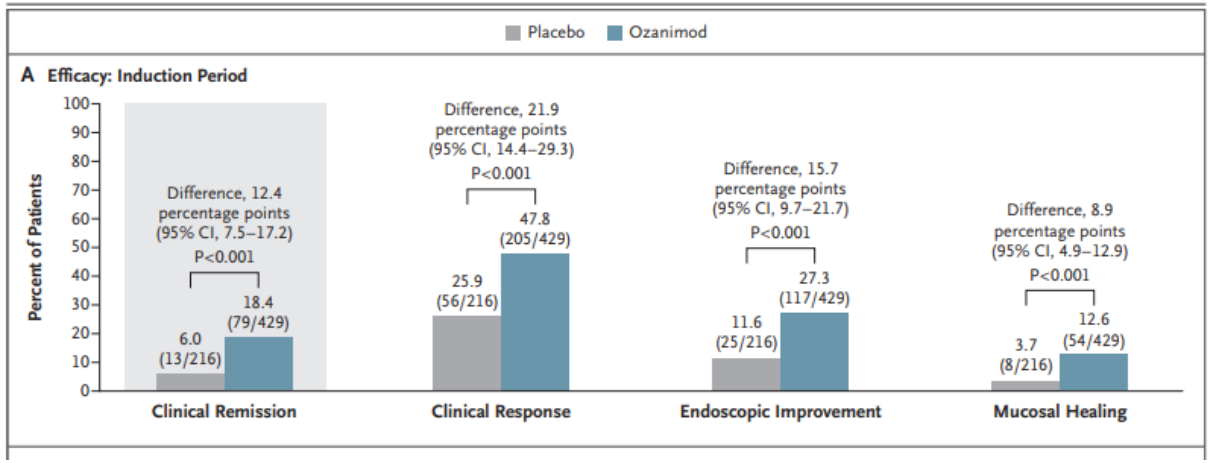
1. Regulates lymphocyte tracking in the gut
2. Regulates vascular tone, HR and cardiac replolarization

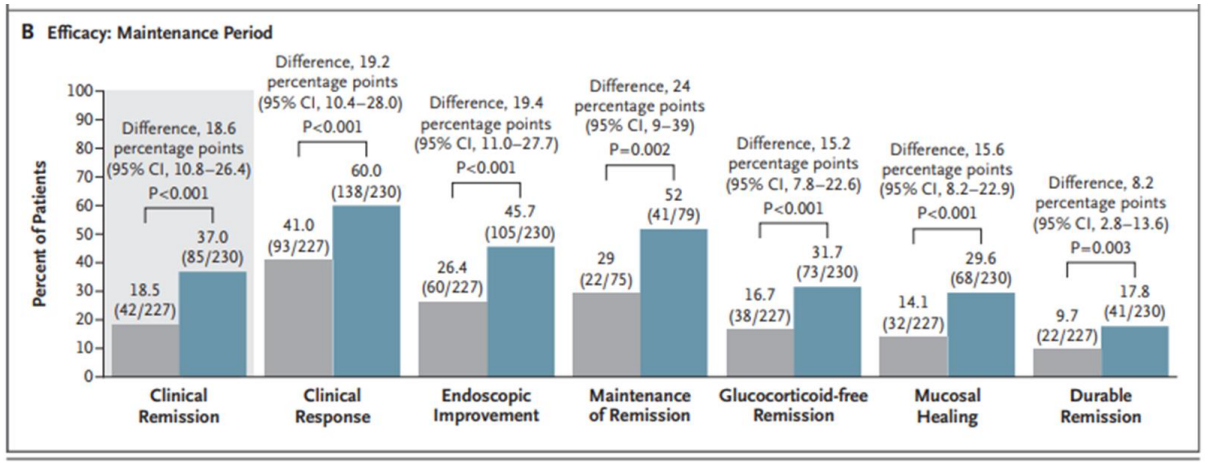
NB - Washout period

Sands B et al. Journal of Crohn's and Colitis, 2023, XX, 1–14

True North- Induction and Maintenance

- 52-Week
- Phase 3 trial double blind RCT
- N- 1831
- Induction-slow dose escalation
- Primary outcomes- clinical remission
  - 10 weeks- 18.4% vs 6%
  - 42 weeks- 37% vs 18.5%





Sandborn WJ et al. N Engl J Med 2021;385:1280-91

True North- Safety

- Ozanimod was generally well tolerated - (SAEs) occurred in ≈ 5%
- TEAEs was similar between Ozanimod and placebo during the induction period but higher with Ozanimod than placebo during the maintenance period
- AEs of special interest (AESIs)
  - based on prior association with S1P receptor modulation
  - generally low in incidence and/or manageable and transient
  - Abnormal LFT /Infections/ Cardiac-related events
  - NB- Patients with recent, clinically significant CVD -not included in the study
- Minimal discontinuation of treatment due to AEs-1-4%

Sandborn WJ et al. N Engl J Med 2021;385:1280-91

Sphingosine- 1 phosphate (S1P) receptor modulators - Ozanimod

Contraindications

- Cardiac
- Strokes or TIA
- Active malignancy or infection
- Advanced liver disease
- Concomitant use of an MAO inhibitor
- Severe untreated sleep apnoea
- Current pregnancy

Monitoring

- Baseline ECG/FBC/LFT
- Ophthalmic examination of the fundus and macula
- VZV antibody test/or confirmed vaccination
- Monitor BP monthly for 3 months
- Regular FBC/LFT monitoring

Conclusion

- There has not been a more exciting time in the treatment of IBD
- These complex diseases offers many challenges, but great opportunity to improve patients' quality of life and outcomes.
- Targeted therapies currently on the market employ a variety of different MOAs
- The IBD pipeline continues to expand at a remarkable rate
- Future prospects???