OneGI

SECOND ANNUAL GI & LIVER *Summit*

Overview of IBD Therapies

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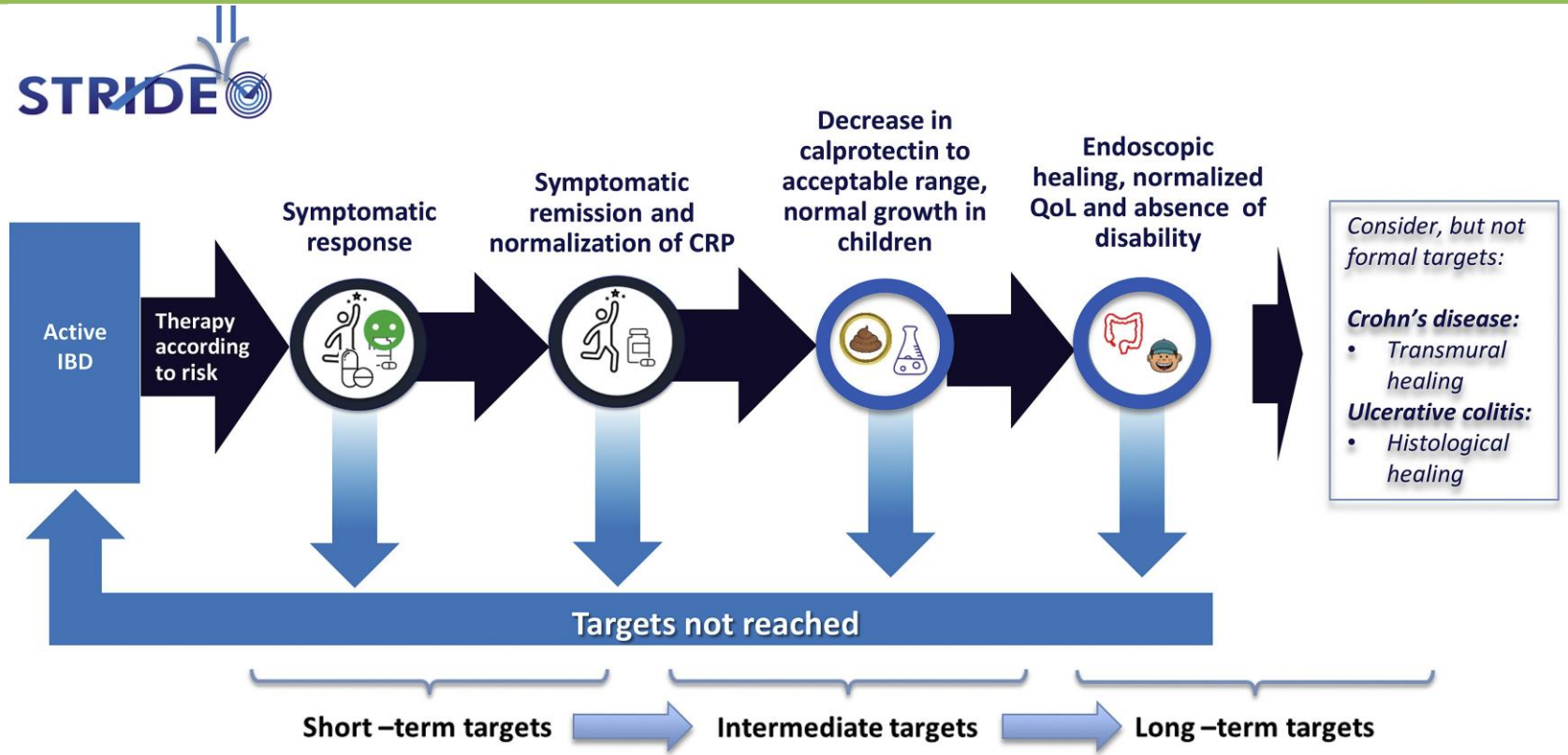
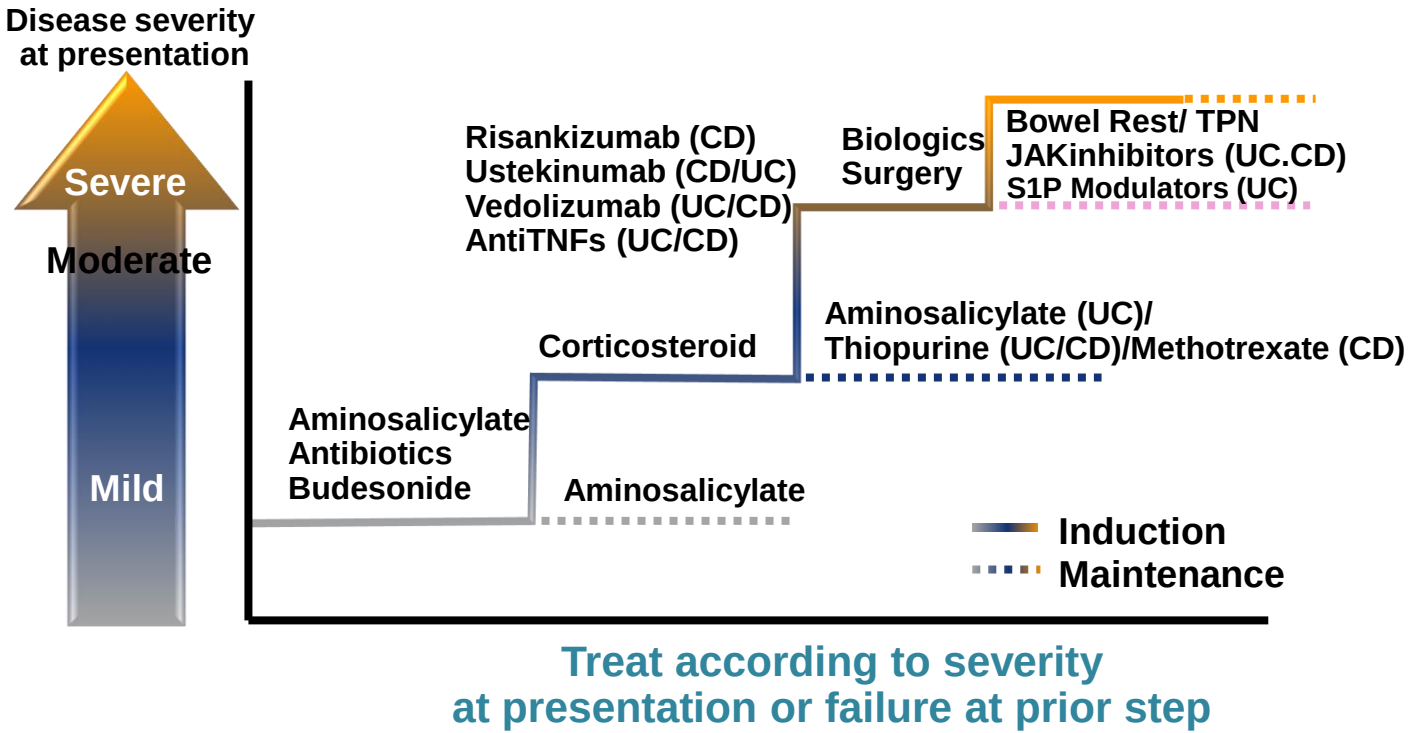
STRIDE II Guidelines: Treat to Target



Dan Turner et al. *Gastroenterology.* 2021 1601570-1583DOI: (10.1053/j.gastro.2020.12.031) Volume 160 Issue 5 Pages 1570-1583 (April 2021).

Therapies Based on Disease Severity



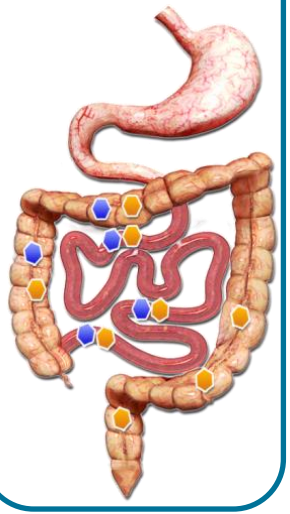
Hanauer SB. *Inflamm Bowel Dis.* 2009.

5-Aminosalicylates

Aminosalicylates: Mild to Moderate UC; ?CD

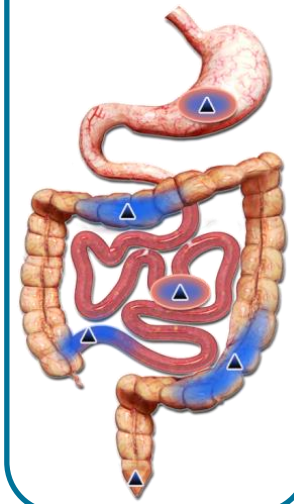
Colon

- Sulfasalazine
- Olsalazine
- Balsalazide



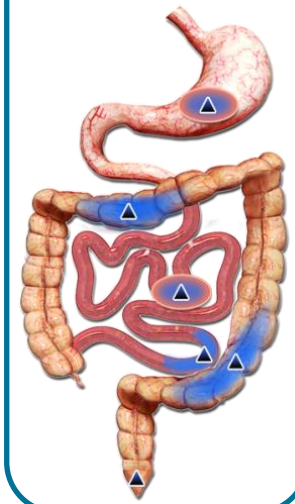
Terminal Ileum
Colon
(release at pH ≥7)

- Delayed-release mesalamine
- MMX® mesalamine



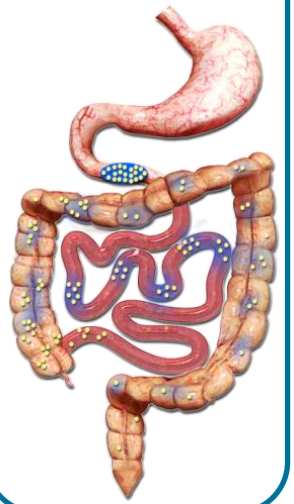
Terminal Ileum
Colon
(release at pH ≥6)

- Granulated mesalamine



Duodenum
Ileum
Colon

- Controlled-release mesalamine



Consider rectal treatments:

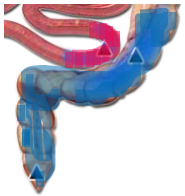
- **Combination better than monotherapy**
- **First-line for proctitis**

Ideal for:

- Tenesmus
- Urgency
- Rectal pain
- Incontinence
- Bleeding
- Paradoxical constipation

Suppository
10-15cm

Enema
40-50cm



Baumgart DC et al. *Lancet*. 2007; Sandborn WJ. *J Clin Gastroenterol*. 2008.

5-Aminosalicylates (5-ASAs)

- Dosing: minimum 2g/day, 4.8g max; Once daily = divided dosing
- MECHANISM: Modulate inflammatory cytokine production, decrease transcriptional activity of nuclear factor-kappa ß (NF-κ ß), inhibit production of prostaglandin and leukotrienes Topical contact with inflamed mucosa required;
- Side Effects:
  - Hypersensitivities – discontinue
  - Sulfasalazine: (sulfa): nausea, allergy, * reversible hypospermia, decreased sperm motility
- Monitoring
  - BUN and creatinine, given rare idiosyncratic cases of interstitial nephritis

Egan LJ et al. *J Biol Chem.* 1999;274(37):26448-26453; Wang YJ et al. *Cochrane Review. DB* 2016; Hanauer S et al. *Cochrane Review.* 2016.

Corticosteroids

Corticosteroids (Induction Only UC & CD)

- Interfere with production of nuclear factor-kappa ß (NF-κ ß), interleukins 1 & 6 and TNF, preventing migration of inflammatory mediators to the GI tract.
- Parenteral, oral, and rectal/ foam formulations
- Optimum dose unclear; prednisone 40mg (0.5-0.75mg/kg/day) for acute symptoms; 60mg have moderately more efficacy but at higher side effects
- Budesonide exhibits 90% first-pass metabolism, to treat local activity
- Budesonide MMX induced clinical and endoscopic remission in 17.7% of mild to moderate UC vs 6.2% receiving placebo by 8 weeks
- Budesonide (enteric coated) 9mg daily is superior to placebo in induction of symptomatic remission in mild to moderate Crohn's disease (terminal ileum/ right colon)
- Systemic steroid higher efficacy rates than budesonide

Goulding NJ et al. *Curr Opin Pharmacol.* 2004;4(6):629-636; Ford AC et al. *Am J Gastroenterol.* 2011;106(4):590-599;
Vavricka SR et al. *Drugs.* 2014;74(3):319-324; Seibold F et al. *J Crohns Colitis.* 2014;8(1):56-63;
Mulder CJ et al. *Eur J Gastroenterol Hepatol.* 1996;8(6):549-553; Zeng J et al. *J Gastroenterol Hepatol.* 2017;32(3):558-566.

Corticosteroids: Side Effects

<u>Have an Exit Strategy</u>!

- Initiate maintenance therapy
- Taper off:
  - 5-10mg/week until 20mg then
  - Reduce by 2.5 to 5mg/week

Antibiotics

Antibiotics (CD)

- Immune response to flora may drive inflammation in Crohn's disease
- No role in UC
- **Ciprofloxacin**
  - Similar efficacy to mesalamine
  - No more effective than placebo for induction of remission

  Metronidazole
  - No more effective than placebo

  Antimycobacterial agents
  - No more effective than placebo

Lichtenstein GR et al. *Am J Gastro.* 2018;113(4):481-517.

Immunomodulators

Immunomodulators (CD & UC Maintenance Only)

- **Thiopurines (CD & UC)**: azathioprine (AZA) & 6-mercaptopurine (6-MP) Purine antagonists; Cause DNA damage, cell-cycle arrest, cytotoxicity, and apoptosis
  - **Methotrexate (CD only):** Converts to methotrexate-polyglutamate→ blocks de novo purine synthesis and dihydrofolate reductase, resulting in reduced inflammation and increased apoptosis

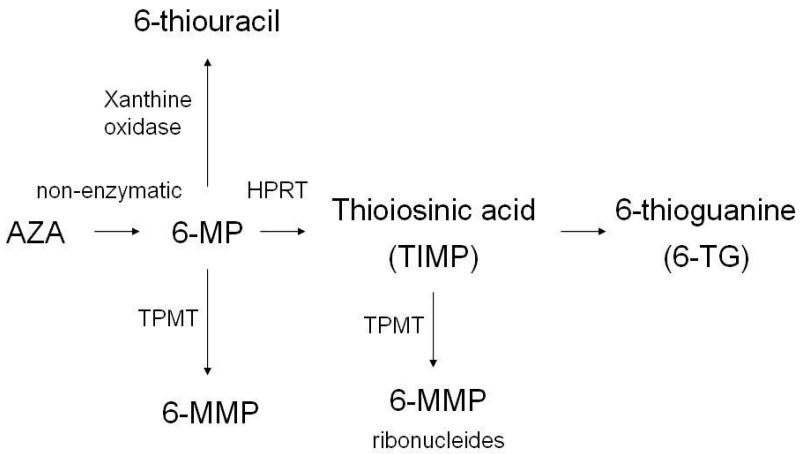
	Azathioprine	6-Mercaptopurine	Methotrexate
Dosage	2.0-2.5mg/kg/day	1.0-1.5mg/kg/day	15-25mg/week + folic acid (5-10mg/week)
Route of Administration	Peroral	Peroral	Subcutaneous injection>> oral
Dosing Intervals	Daily or bid	Daily or bid	Once weekly

Neurath MF et al. *Clin Gastroenterol Hepatol.* 2005;3(10):1007-1014; Goldman ID et al. *Pharmacol Ther.* 1985;28(1):77-102; Grim J et al. *Clin Pharmacokinet.* 2003;42(2):139-151.

AZA and 6-MP: Metabolism

- Check TMPT enzyme activity prior to starting
- Risk of myelosuppression if elevated 6-TGN
  - 89% normal or high TPMT activity (Normal dose)
  - 10% heterozygous mutation → low TPMT activity (1/2 dose)
  - 0.3% homozygous mutation → negligible TPMT activity (DO NOT PRESCRIBE!)
- *NUDT15 R139C* variation: induce leukopenia in Asians
- **Check CBC & liver enzymes every 3 months**

Target the 6TGN!

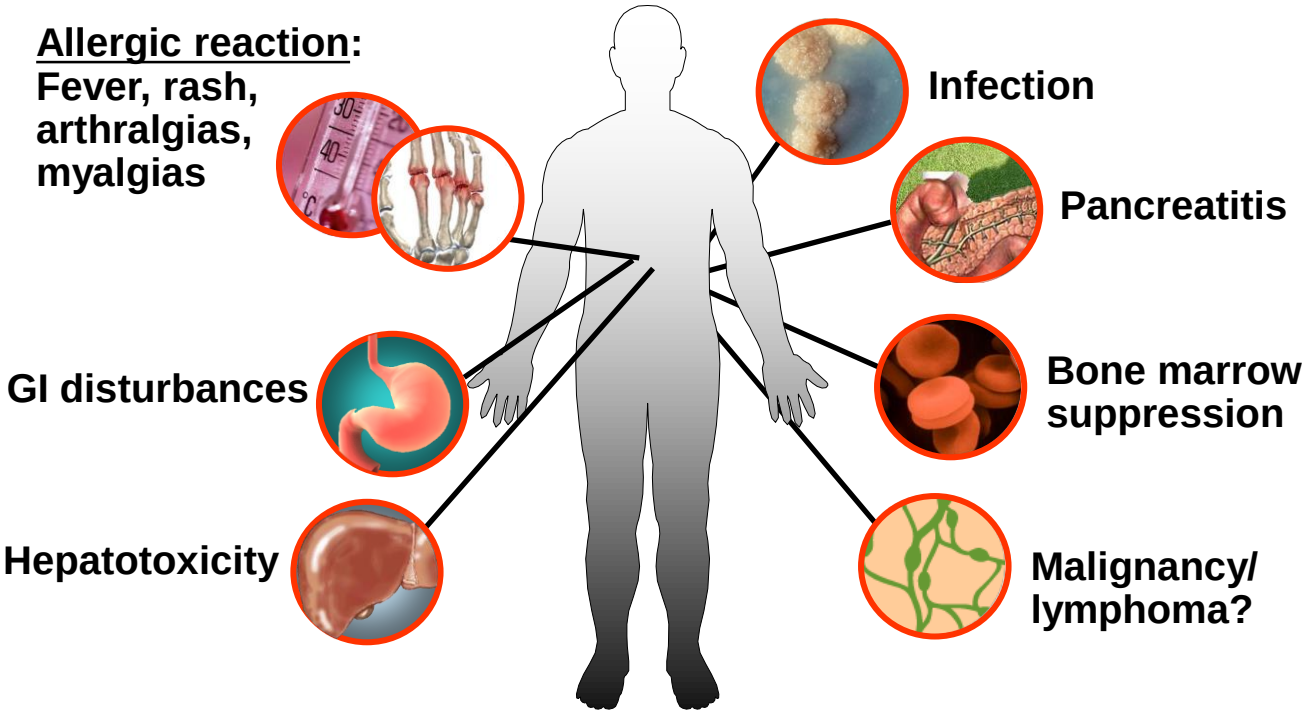


Patients with 6-TGN levels above threshold of 230-260 had a 3-fold odds of being in remission

Remission rates:
Over threshold = 62%
Below threshold = 36%

Osterman MT et al. *Gastroenterology*. 2006;130(4):1047-53.

Adverse Effects of Azathioprine/6-Mercaptopurine



Kornbluth A, Sachar DB. *Am J Gastroenterol*. 2004;88:1371; deBoer N et al. *Nature Clin Pract Gastroenterol Hepatol*. 2007;4:686.

Methotrexate: Side Effects

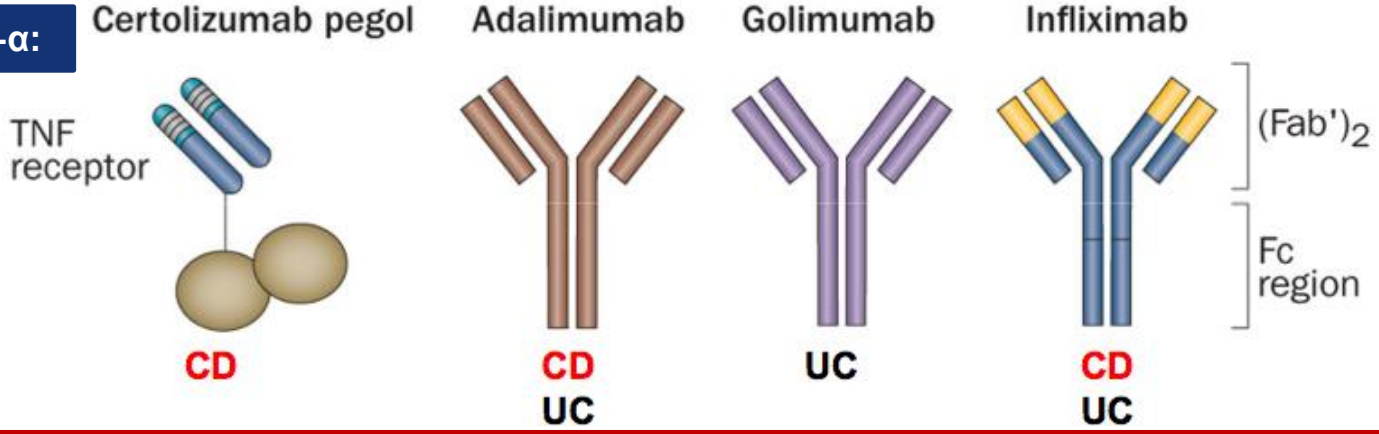
- GI distress: nausea/vomiting*
- Mouth sores*
- Headache*
- Fatigue*
- Myelosuppression
- Hepatitis
- Pulmonary fibrosis
- Infection

**Can be reduced or alleviated with folate supplementation*

Biologics: Anti-TNF-α Agents

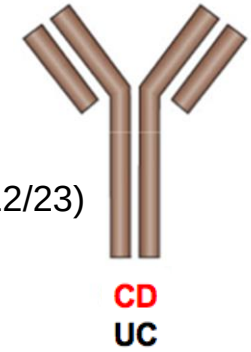
Biologics in IBD: Moderate to Severe Disease

Anti-TNF-α:

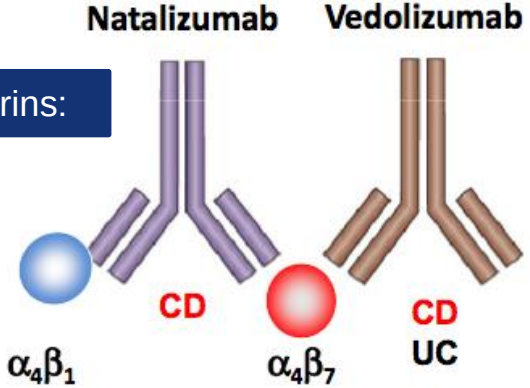


Anti-interleukins:

Ustekinumab (UC/CD) (anti- IL12/23)
Risankizumab (CD) (anti-IL23)



Anti-integrins:



To Combo or Not to Combo?

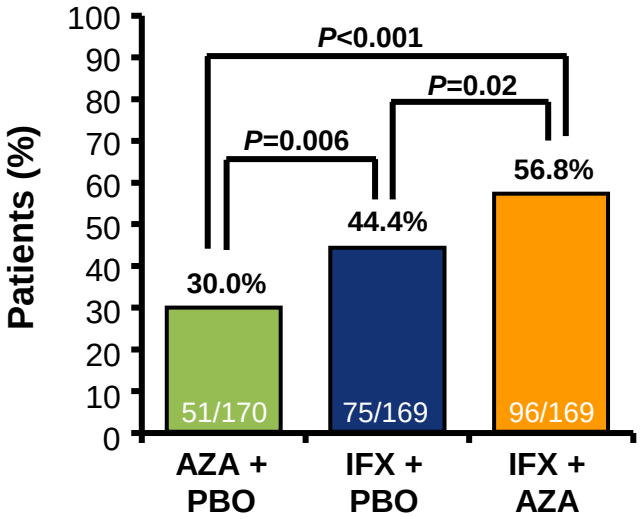
To Combo:

With Anti-TNFs:

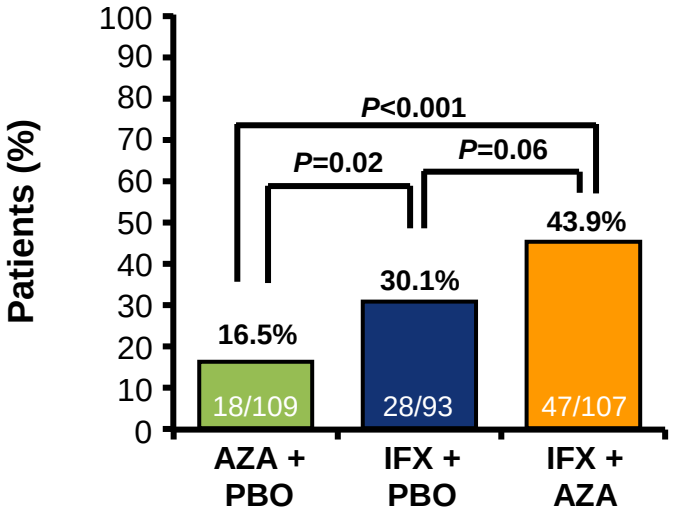
- Severe/ Penetrating / Perianal Disease
- Low drug levels
- Prior anti-drug antibody formation.
  - With continuous use
  - With non-adherence

Comparative Effectiveness in CD (SONIC)

Clinical Remission



Mucosal Healing



Colombel JF et al. *N Engl J Med*. 2010;362:1383.

To Combo or Not to Combo?

Not To Combo:

With Anti-TNFs:

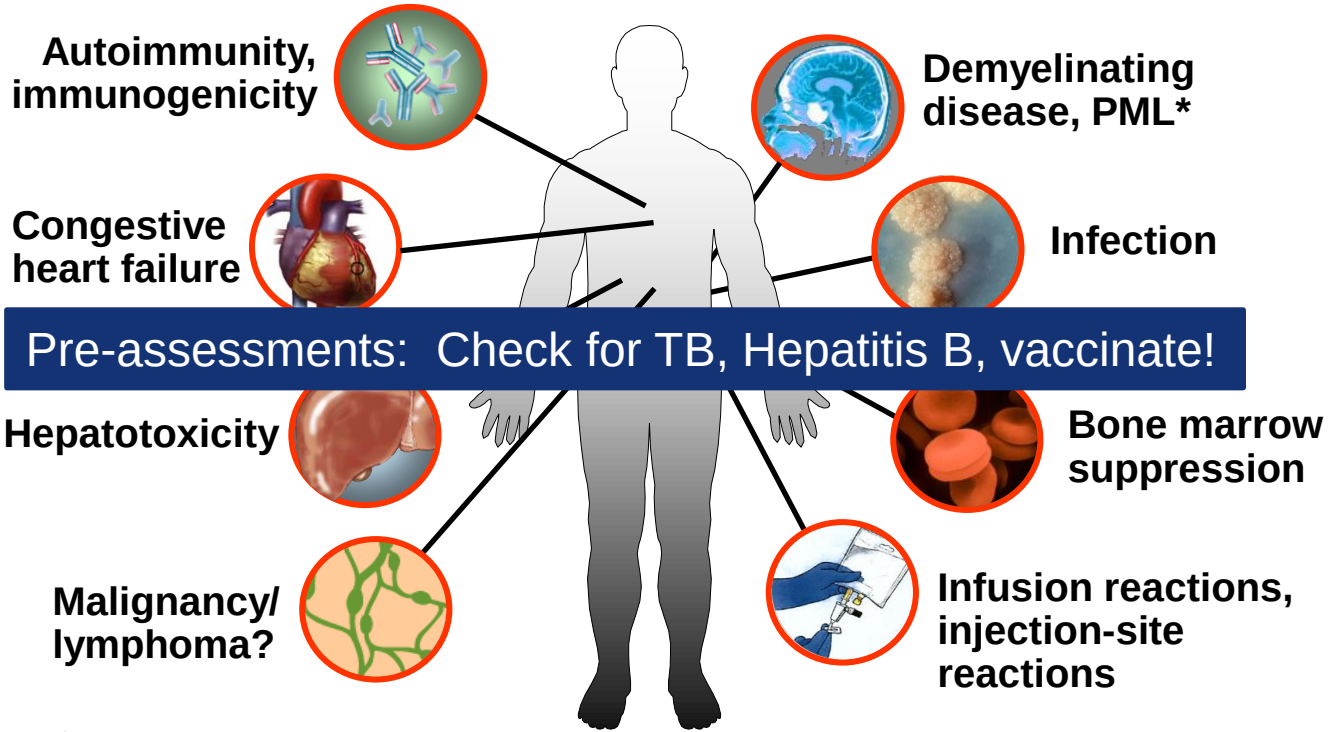
- Great levels
- Remission

With Ustekinumab

With Risankizumab

With Vedolizumab

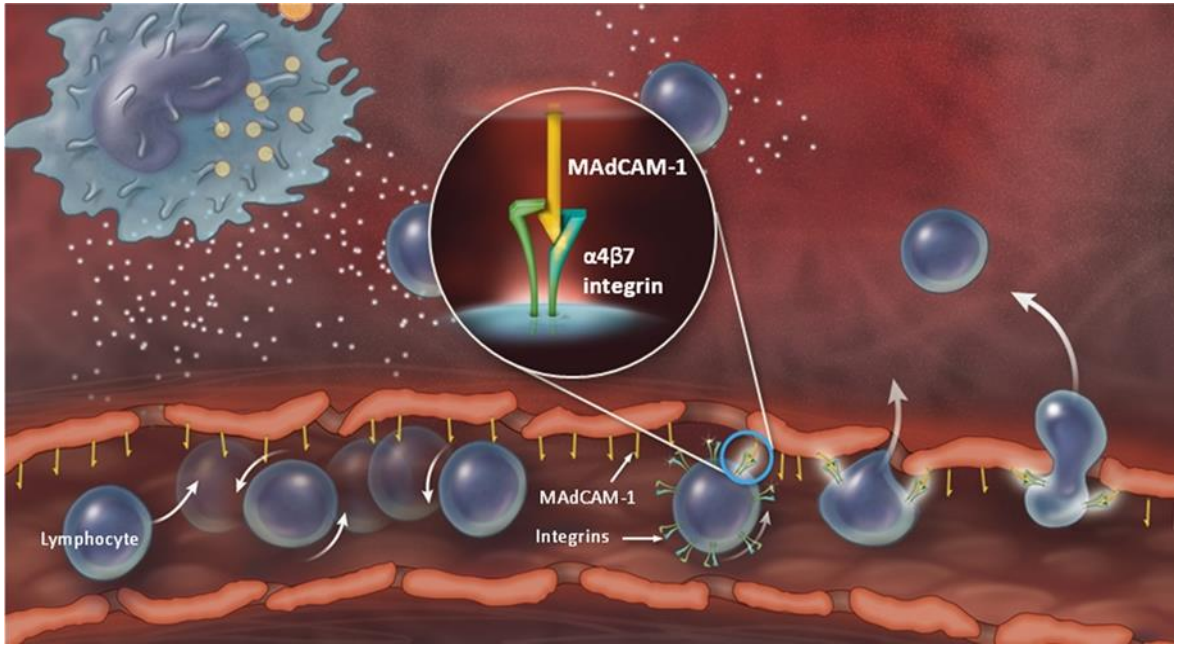
Adverse Effects of Biologics



*Reported with natalizumab.
PML, progressive multifocal leukoencephalopathy.
Clark M et al. *Gastroenterology*. 2007;133:312; Tysabri (natalizumab) [package insert]. South San Francisco, CA: Elan; Jan 2008.

Biologics: Anti-Integrins

Vedolizumab for UC & CD



- No increased risk of infections (*C diff*, TB, sepsis < 0.6% patients)
- No PML risk compared to natalizumab
- < 5% infusion reactions
- Low immunogenicity

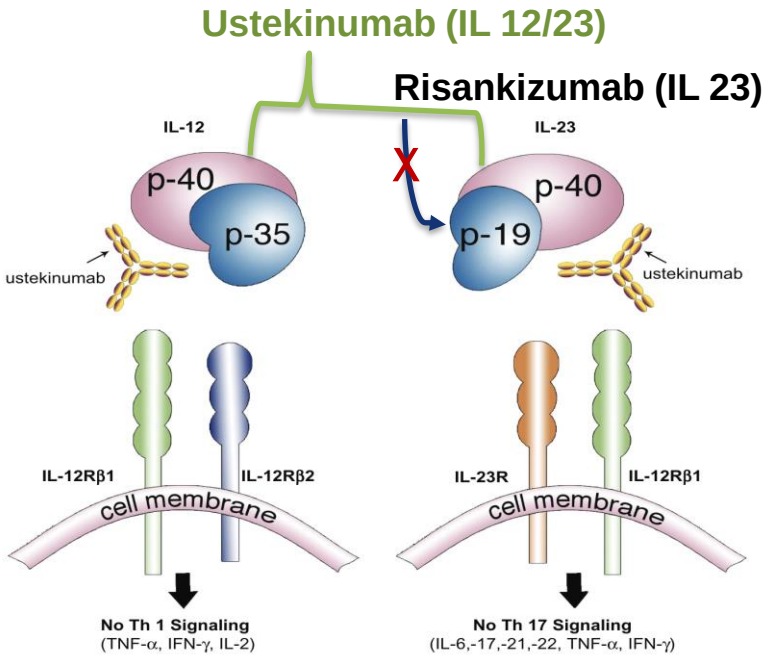
IgG1 mAb to α4β7 integrin

Modulates gut, NOT brain lymphocyte trafficking

Biologics: Anti-IL 12/23

Anti-p40/p-19 Agents for IBD

- **Ustekinumab (UC & CD) (IL 12/23) & Risankizumab (CD) (IL 23)**
- IV Induction and SQ maintenance
- **Good safety profile ~ to placebo**
- Pre-assess for TB and hepatitis
- Concomitant immunomodulators not needed
- Low immunogenicity

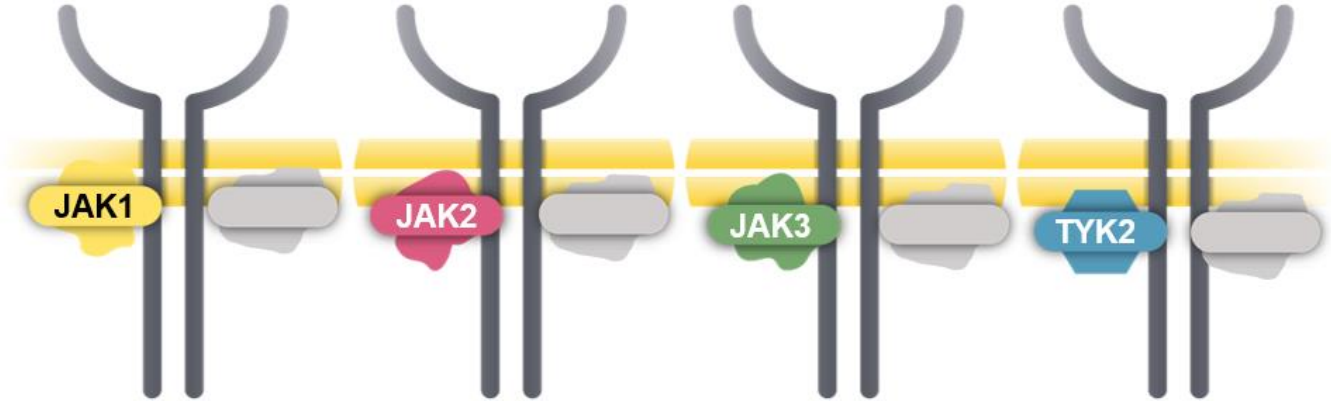


Koutruba N et al. *Ther Clin Risk Manag*. 2010;6:123-141.

Small Molecules

JAK inhibitors: Protein Tyrosine Kinases

Composed of 4 Isoforms: JAK1, JAK2, JAK3, and TYK2



JAK1 is predominantly involved in inflammatory and innate immune responses[6] and is expressed on the myeloid and stromal compartments of intestinal mucosa[2]

JAK2 has broad functions, from hematopoiesis to growth and neural development[4-7]

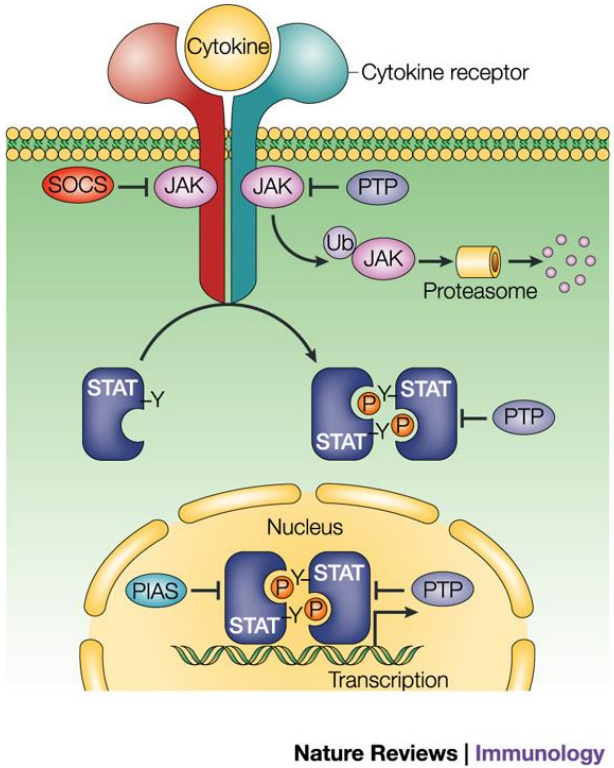
JAK3 expression has been linked to lymphocyte proliferation and immune homeostasis[2,4,6]

TYK2 has been linked to antiviral responses[4,6]

1. Jamilloux Y, et al. *Autoimmunity Rev*. 2019;18:102390. 2. Salas A, et al. *Nat Rev Gastroenterol Hepatol*. 2020;17(6):323-337. 3. Soendergaard C, et al. *Pharmacol Ther*. 2018;192:100-111.
4. O'Shea JJ, et al. *N Engl J Med*. 2013;368(2):161-170. 5. Clark JD, et al. *J Med Chem*. 2014;57(12):5023-5038. 6. Traves PG, et al. *Ann Rheum Dis*. 2021;80(7):865-875.
7. Parmentier JM, et al. *BMC Rheumatol*. 2018;2:23.

JAK Inhibition

- Oral molecules
  - Inhibits cytokine signaling (JAK/STAT pathway)
  - Mediates cellular response to these cytokines
- Metabolized by liver
- Adverse Effects:
  - LDL&HDL elevation.
  - Herpes Zoster → VACCINATE!
  - Pregnancy Category [C]: animal studies concerning (@6x dose); minimal human data.
  - **?Thrombosis/ MACE/ Cancer risk – RA high dose study.**
- Pre-assess: TB, Hep B
- Monitor CBC, LFTs



Shuai K et al. *Nat Rev Immunol*. 2003;11:900.

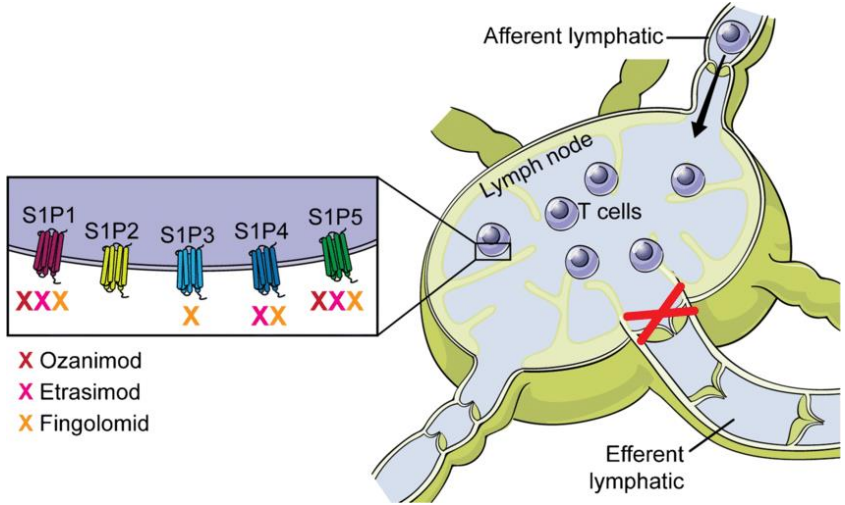
JAKi Overview

- Tofacitinib (UC) (JAK1,3)
  - Induction: 10mg BID or 22 XR QD
  - Maintenance 5mg BID or 10mg XR QD
- Upadacitinib (UC, CD) (JAK1 inhibition)
  - Induction: 45mg daily (UC: 8 weeks; CD: 12 weeks)
  - Maintenance: 30mg daily (highest efficacy) 15mg daily (also option)
- After antiTNF failure or intolerance.
- Rapid onset! (days to weeks)

Danese S et al. *Lancet*. 2022 Jun 4;399(10341):2113-2128; Ytterberg S et al. *N Engl J Med*. 2022 Jan 27;386(4):316-326. https://www.fda.gov/drugs/drug-safety-and-availability/fda-requires-warnings-about-increased-risk-serious-heart-related-events-cancer-blood-clots-and-death

S1P Inhibitor for Ulcerative Colitis

- **Ozanimod (S1P1 and S1P5)**
- **Contraindicated: Recent MI, CHF, AV block, untreated OSA, or taking MAO inhibitor**
- Pre-assess: baseline EKG, CBC, LFTs
- **AEs: Macular edema, hypertension**
- No immunogenicity
- Approved for Multiple Sclerosis
- Monitor vision if high risk (h/o macular edema, DM, etc.)
- Consider positioning after mesalamine/ 5-ASA failure

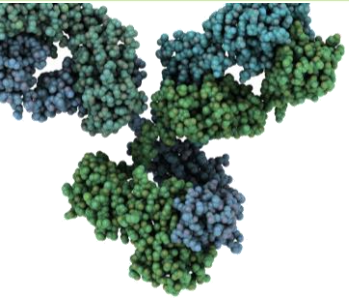


Titration doses: 1st week
Then: 0.92 mg daily

MI = myocardial infarction; CHF = congestive heart failure; AV = atrioventricular; OSA = obstructive sleep apnea; MAO = monoamine oxidase; AEs = adverse effects.

Shukla T et al. *Curr Gastroenterol Rep*. 2019;21(5):22.

Biosimilars



Infliximab (REMICADE)

Biosimilar Name	Approval Date
Avsola (infliximab-axxq)	2022
Ixifi (infliximab-qbtx)	2019

Adalimumab (HUMIRA

Biosimilar Name	Approval Date
(adalimumab-adaz)	October 2018
Cyltezo (Adalimumab-adbm)	August 2017
Amjevita (Adalimumab -atto)	September 2016

No significant differences in clinical outcome, loss of response, adverse events, or immunogenicity

https://www.fda.gov/drugs/therapeutic-biologics-applications-bla/biosimilars;
https://www.fda.gov/drugs/biosimilars/biosimilar-product-information
Raffals et al. *Clinical Gastroenterol and Hepatology.* April 2019.

Key Takeaways

- Recently approved treatments can help personalize IBD care.
- Utilize shared decision making on treatment based on disease-related, medication-related, & patient-related factors.
- Achieve mucosal healing to prevent complications, consider deeper transmural & histologic healing to impact long-term outcomes.