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2021 Fourth Annual National Conference

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Red Rock Hotel – Las Vegas, NV

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Positioning Biologics in IBD

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Disclosures

Gabriella McCarty NP-C

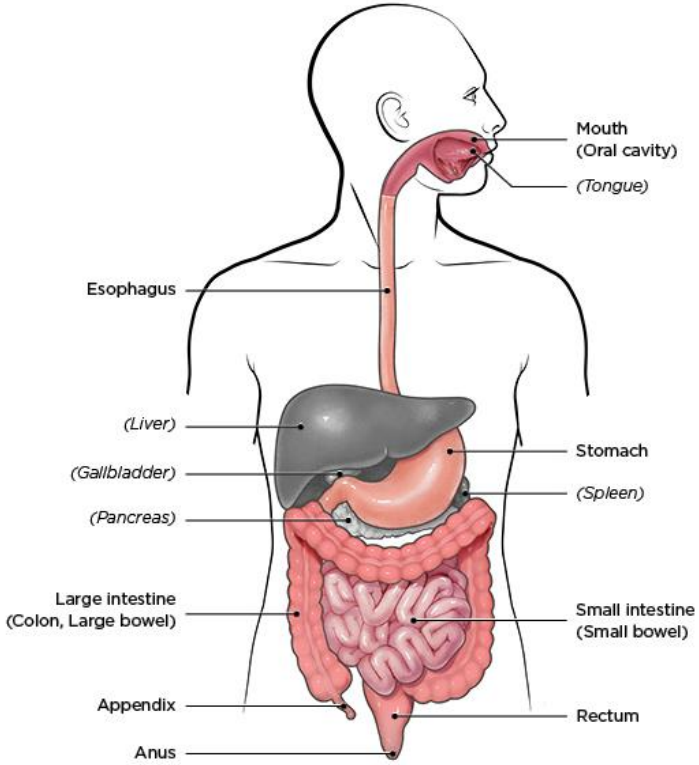
Speakers Bureau: Abbvie, Clinical Area – IBD

Speakers Bureau: Pfizer, Clinical Area – IBD

Speakers Bureau: Janssen, Clinical Area – IBD

Objectives

- Discuss the need for patient education on disease state, chronicity, severity, location
- Discuss treatment risks and benefits but also risks of not being treated
- Review different medications
- Future of IBD treatment



Crohn’s Disease (CD) Vs. Ulcerative Colitis (UC)

Crohn’s Disease may affect any part of the digestive system from mouth to anus. All layers of the lining of the bowel may be inflamed.

Ulcerative Colitis affects the large intestine, which is made up of the rectum and colon. Only the inner lining of the bowel is inflamed.

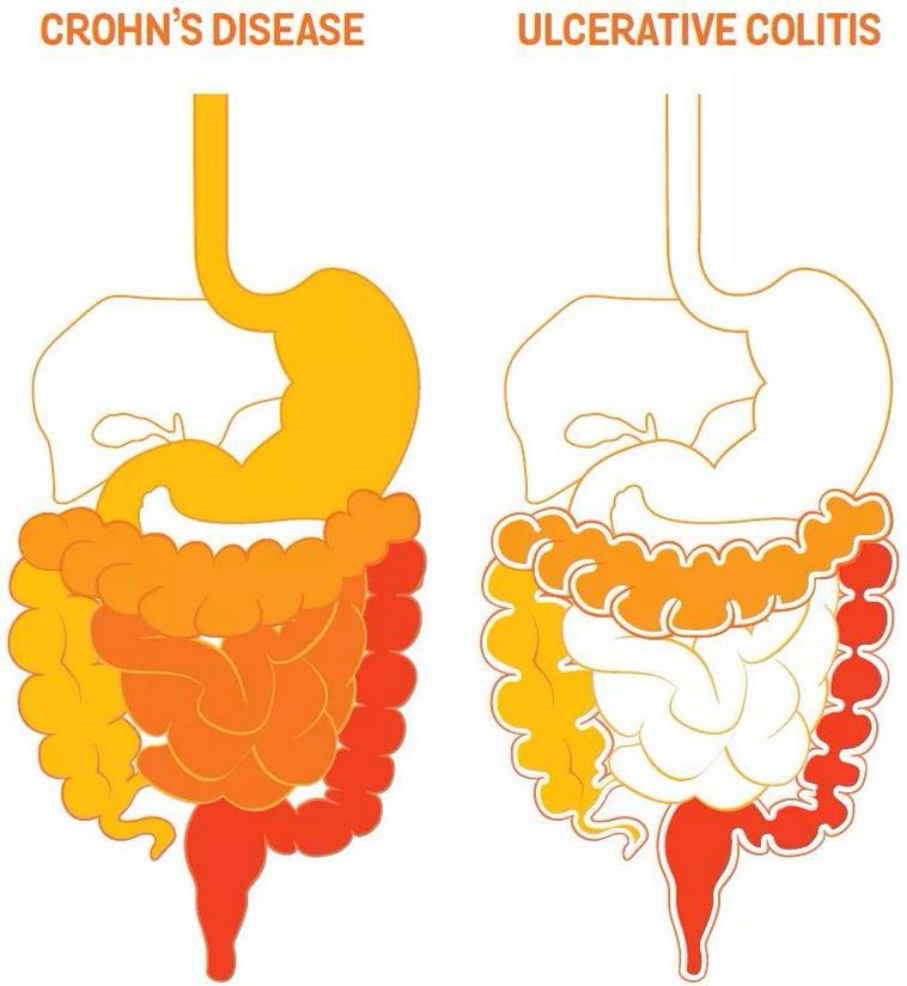


Image obtained from guidelinesinpractice.co.uk.

IBD Characteristics

CD Symptoms

- Frequent diarrhea
- Abdominal pain
- Rectal bleeding
- Weight loss
- Fever
- Fatigue
- Fistulas, perianal disease, abdominal abscess, SBO, peritonitis
- Malabsorption
- Anemia
- Less common- UGI Crohn's – mouth ulcers, odynophagia, epigastric pain, N/V

UC Symptoms

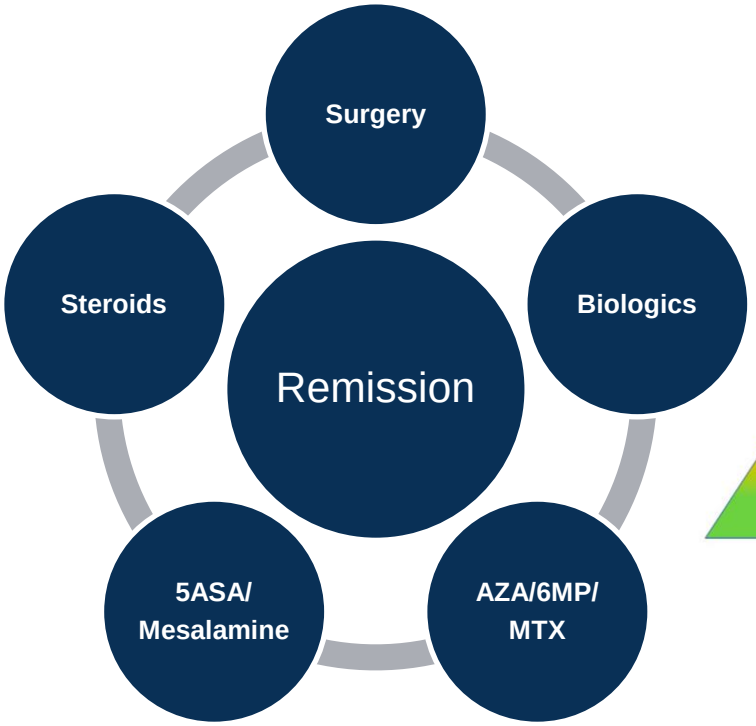
- Frequent diarrhea
- Abdominal pain/cramping
- Blood in stool
- Tenesmus
- Fatigue

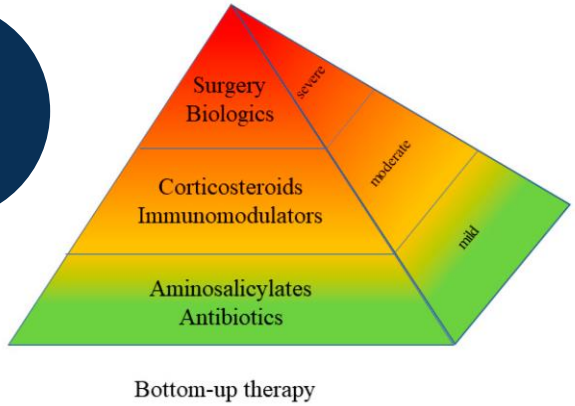
Extraintesinal manifestations can affect the skin, joints, eyes, etc

- Arthritis/arthropathy- 20%
- Uveitis/iritis/scleritis- 5%
- Erythema nodusum/pyoderma gangrenosum- 10%
- Primary sclerosing cholangitis- 5% of CD, presenting with elevated ALP

Lichtenstein GR et al. *Am J Gastroenterol*. 2018; 113:481-517.

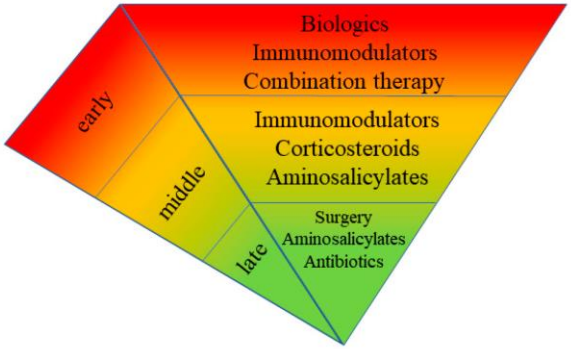
Treatment: Where Do You Start?





Bottom-up therapy

Top-down therapy



Top down therapy superior to conventional therapy

Top up Top Down Image obtained from biomedicines 3 July 2020.

Nakasa H. *Gut and Liver*. Optimizing the Use of Current Therapies and Emerging Therapeutic Approaches to Achieve Therapeutic Success in Patients with IBD. March, 2019.

What Is the Goal?

- Inducing and maintaining remission
  - Concept of disease clearance in UC which is a combination of clinical, endoscopic and histologic remission
  - In Crohn's, may encompass transmural healing on cross-sectional imaging (MR enterography)
- Steroid-free remission
- Achieving these goals may block the progression of the disease in the long term and prevent complications
- Avoid surgery
- Ultimately, patient wants to feel better faster
- Therapy is chosen based on activity, severity, extent of inflammation, prognostic factors

Rubin DT et al. *Am J Gastroenterology*. 2019;114(3):384-413; Colombel J. *Gastroenterology & Hepatology,* 2021, Vol 17, Issue 5, May.

IBD Treatment Is Not Black and White

- Think individualized
- Involving patients in the decision making typically increases compliance rates

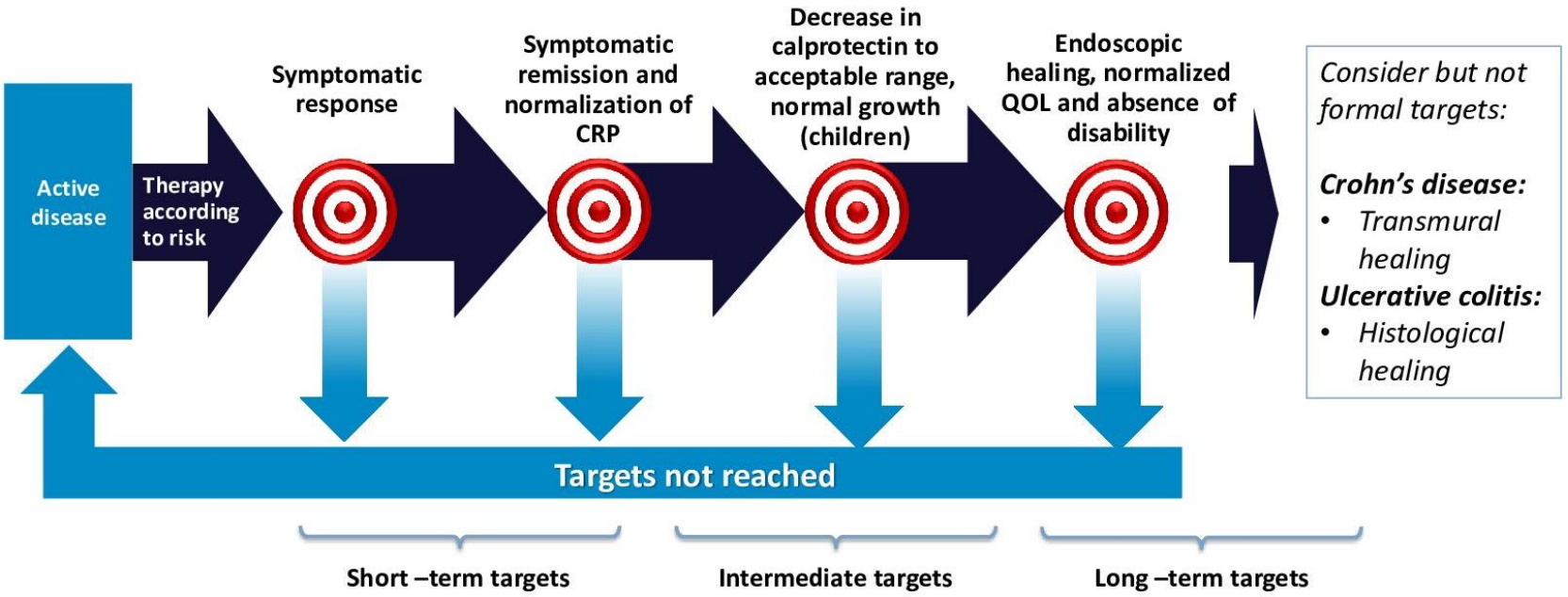
Consider various factors when choosing therapy

- Severity of disease
- Risk factors for severe disease
- Patient preference (injectable vs infusion), ?needle phobia
- Medication history and compliance
- Infection and cancer risk
- Financial situation and insurance coverage
- Distance to infusion center
- Living condition (college dorm)
- Support system

Sandborn W et al. *Gastroenterology & Hepatology*. Vol 17, Issue 4, Suppl 4, April 2021.

Treat to Target

Figure 2: Treatment targets in both Crohn's disease and ulcerative colitis



The management of IBD has evolved from targeting the control of symptoms to targeting the suppression of mucosal inflammation, leading to the concept of "treat to target"

https://pubmed.ncbi.nlm.nih.gov/33359090/;
Nakasa H. *Gut and Liver*. Optimizing the Use of Current Therapies and Emerging Therapeutic Approaches to Achieve Therapeutic Success in Patients with IBD. March, 2019.

Aggressive Therapy Earlier Prevents Aggressive Disease Complications

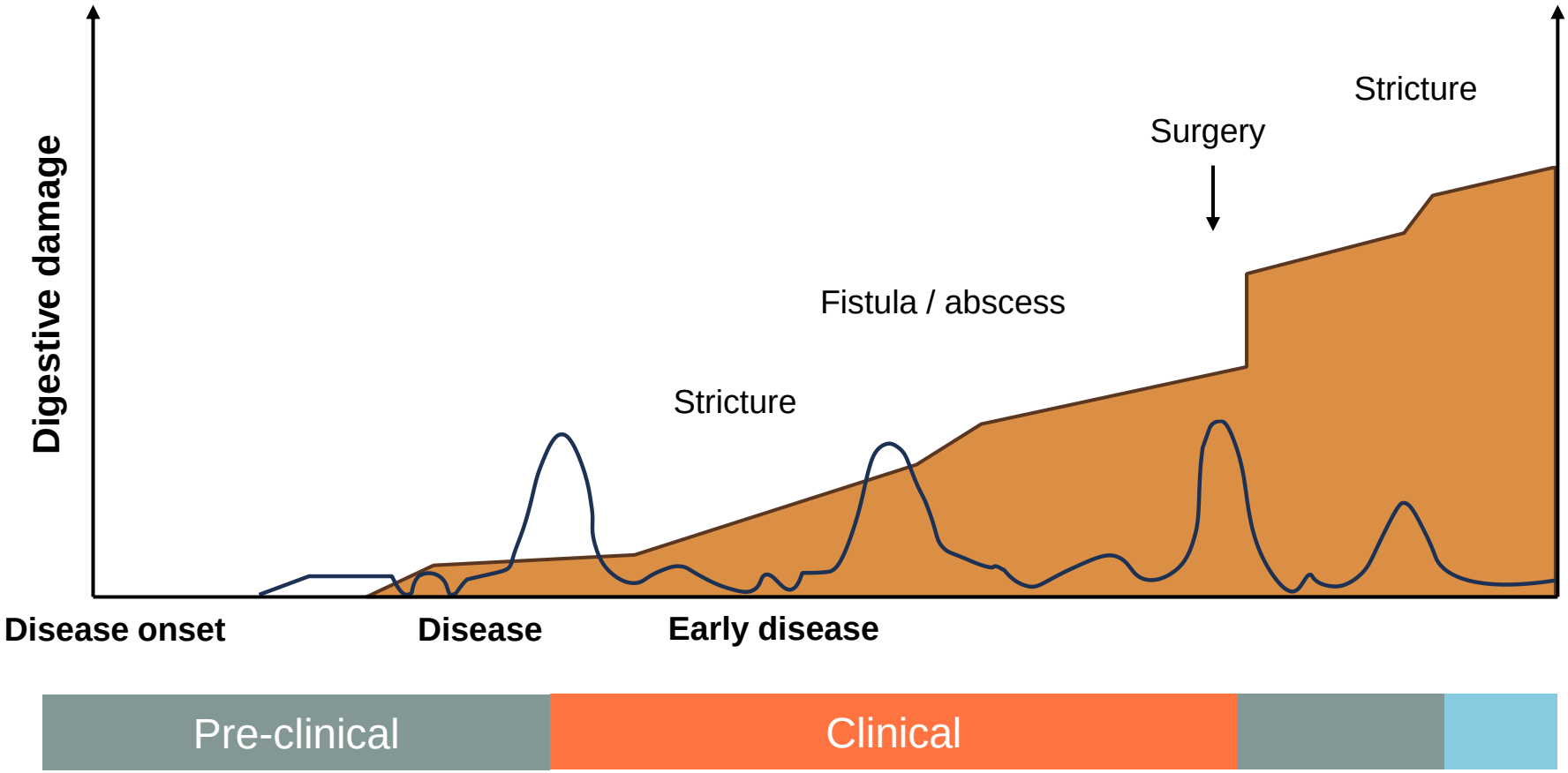


Image obtained from EMJ 16 May 2017, Targeting Disease Progression in Crohn's Disease: Fighting an Unrelenting Enemy.

Predicting Severity

CD- High Risk

- <30 years old
- Deep ulcers
- Perianal disease
- Granulomas per pathology
- Prior surgery
- Stricture/ penetrating disease
- Involvement of UGI tract
- Steroids at first flare up
- Lack of mucosal healing after induction of clinical remission
- Smoking
- Elevated CRP/fecal calprotectin
- Women may have higher risk of needing surgery
- Genetic marker mutations (NOD2/CARD15/ATG16L1/MDR1)

UC- High Risk

- <30 years old
- Deep ulcers
- Pancolitis
- High CRP and ESR
- Steroid use
- Hospitalization
- C. diff
- CMV
- Development of PSC (more common in men)
- Patients with a FHX of IBD have a higher chance of having medically refractory UC and EIMs
- Genetic markers mutations (MDR1)

www.gastro.org/IBDcarepathway;
Yarur et al. *Gastroenterology & Hepatology*. Predictors of Aggressive IBD. Oct 2011: Vol 7, issue 10.

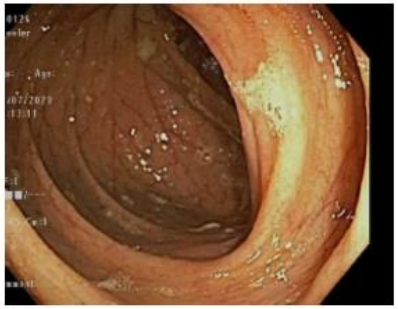
Case Study

- M.W. is a 24 y/o WM first seen in February of 2020 with intermittent bright red blood in his stools x 1 year with occasional diarrhea/constipation
- No past medical or surgical hx, no prior colon
- No FHX of CRC, IBD
- Social: Works as a police office for the City of Cleveland, single
- Saw PCP and DRE was neg
- Med list: MVI, fish oil, biotin, flax seed
- No NSAIDs

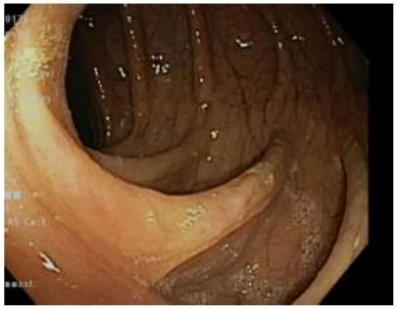
Case Study

- Plan – Colonoscopy, CBC/CMP/ESR/CRP
- Findings – Labs wnl; colon done 3 days after OV showed severe proctitis
- Plan – mesalamine 1000mg supp qhs x 1 week then qohs; repeat FS in 6 months

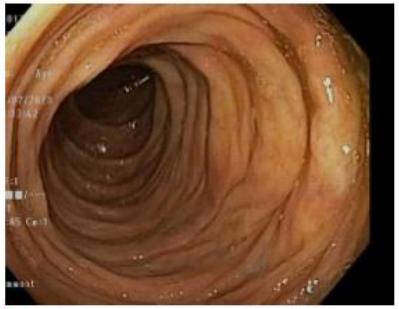
1 Terminal ileum



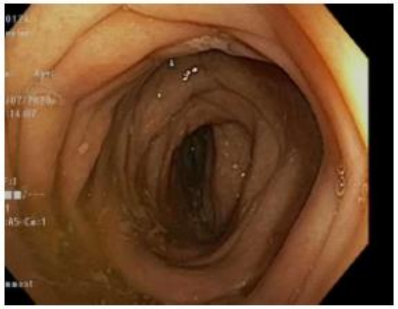
2 Cecum



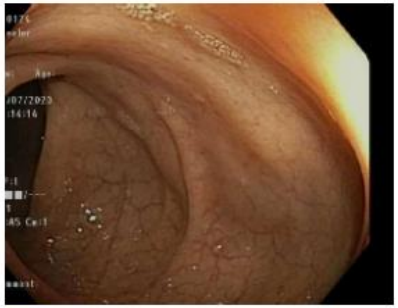
3 Cecum



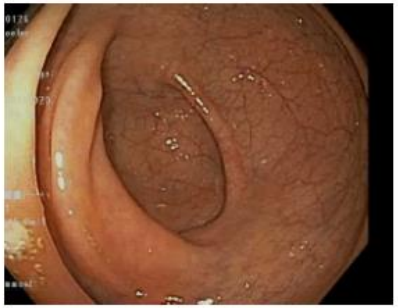
4 Ascending Colon



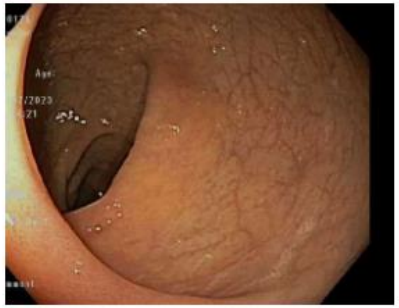
5 Hepatic Flexure



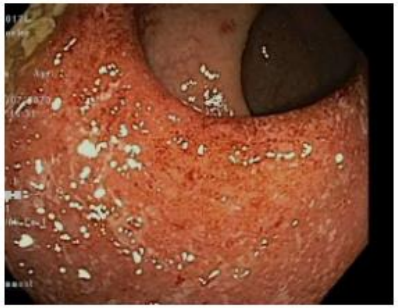
6 Hepatic Flexure



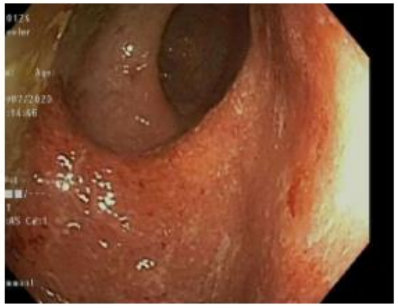
7 Transverse Colon



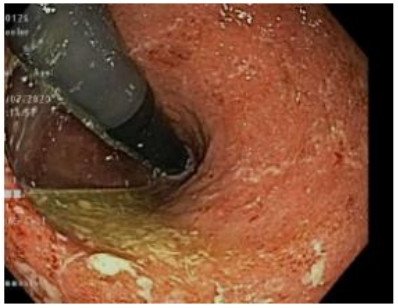
8 Transverse Colon



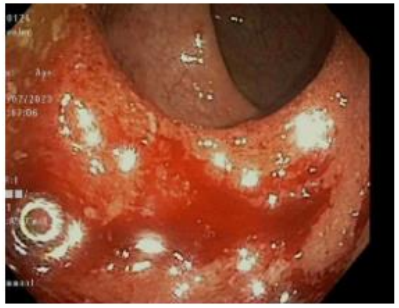
9 Descending Colon



10 Sigmoid Colon



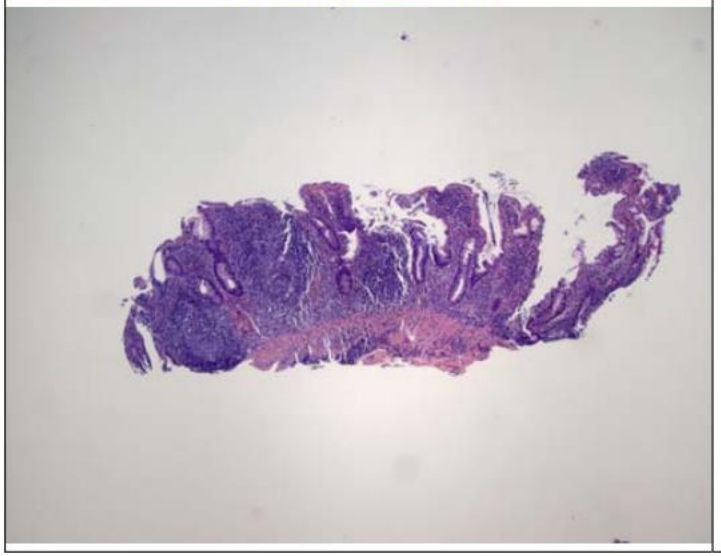
11 Sigmoid Colon



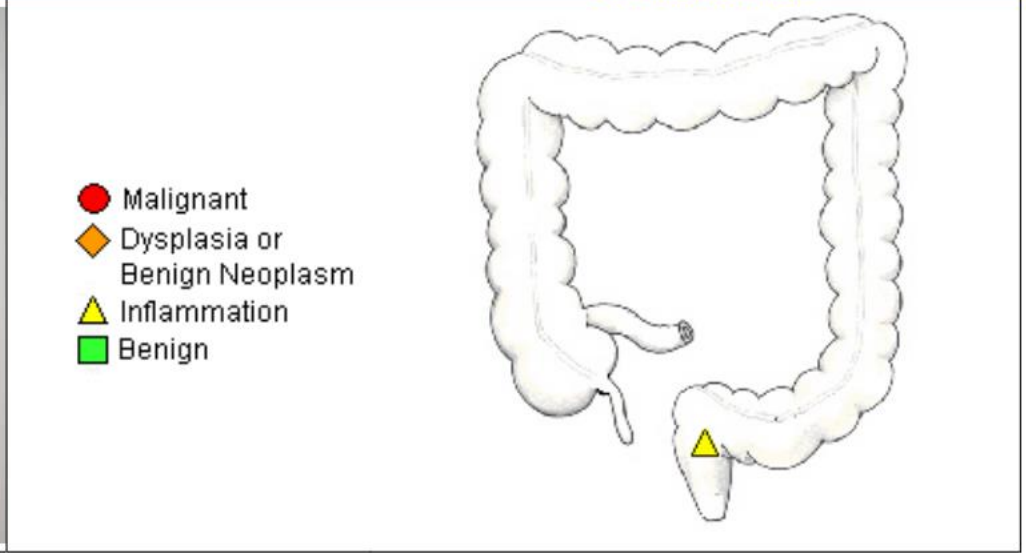
12 Rectum

Case Study – Pathology Findings

PHOTOMICROGRAPH



ORGAN DIAGRAM



DIAGNOSIS

RECTUM, BIOPSIES:

CHRONIC ACTIVE COLITIS WITH ULCER AND REGENERATIVE EPITHELIAL CHANGES.

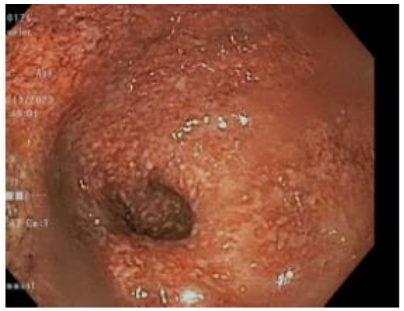
COMMENT: The biopsy consists of several fragments of rectal mucosa with a marked basal lymphoplasmacytosis, crypt architectural disarray and diffuse cryptitis. The findings are highly suspicious for primary inflammatory bowel disease, although clinical and endoscopic correlation is recommended for a definitive diagnosis. There is no evidence of granulomas, dysplasia or malignancy.

Case Study – Fast Forward

- June 2020 – Patient seen in the office for worsening S/S. Turns out he only took the mesalamine supp x 9 days (too expensive), but had felt better with them immediately. Got new insurance and resumed 2 weeks prior to this visit.
- Symptoms: Severe cramps, bloating, bloody diarrhea every hour, nocturnal as well, lost 15#. Mucous in stool.
- Increased stress at work (Cleveland Police Officer, worked 12 straight hours downtown riots on Saturday). Sat fever 102. No temp now. Hardly eating. Past week also using ibuprofen 600mg, 2 daily.

Case Study

- Plan – FS planned for the following day, check CBC/CMP/ESR/CRP and fecal calprotectin. Continue mesalamine 1000mg supp qhs but add Prednisone 40mg PO daily with a taper dose of 10mg weekly. Stop NSAIDs. Fluid/electrolyte replacement.
- Findings – Labs WBC 11.74, H&H 35.6/11.5, PLT 479, Alb 3.3, ESR 54, CRP 11.1, Fecal Cal 1,103.9; Colon showed severe pancolitis UC (Mayo score 3).
- Plan – Increase Prednisone to 60mg, start Remicade 10mg/kg ASAP, Imuran 100mg PO daily, repeat colon in 6 months.



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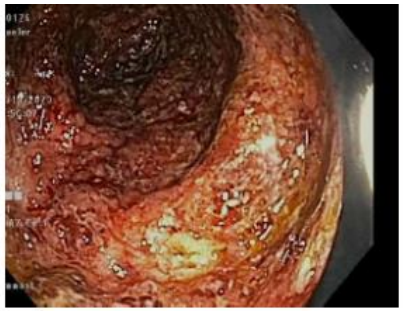
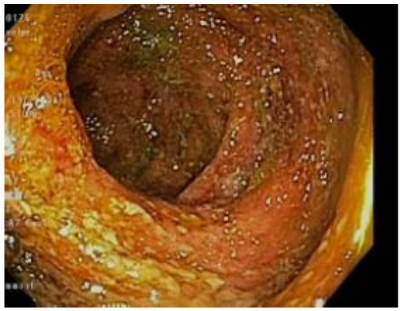


2 Sigmoid Colon



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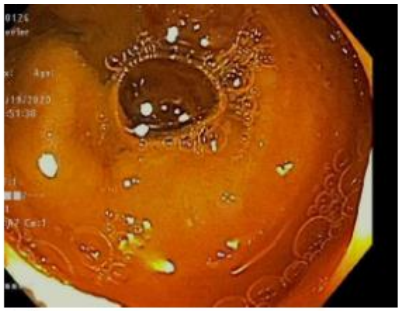
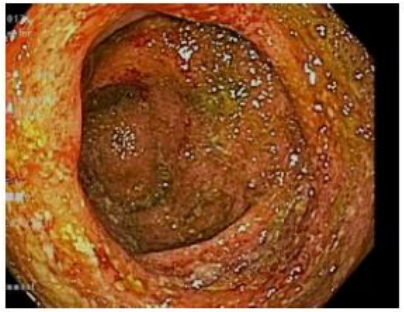
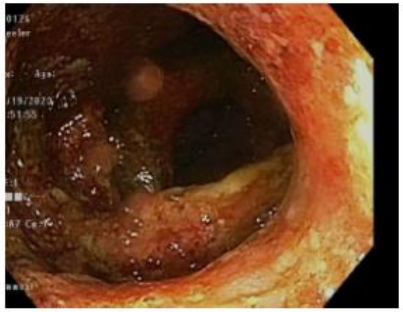


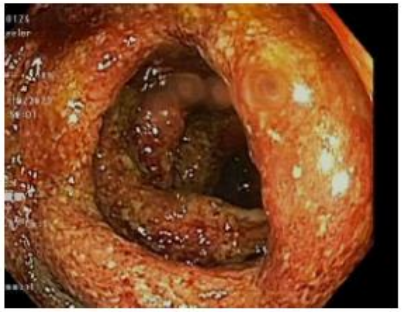
4 Terminal ileum



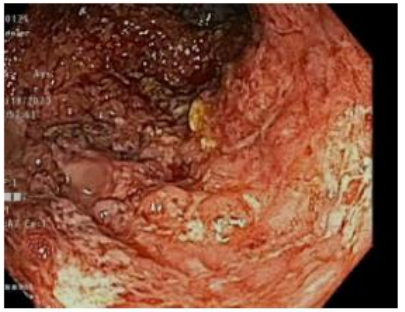
5 Ascending Colon



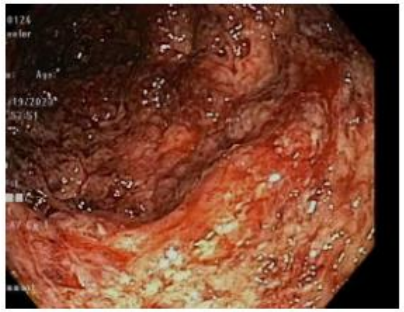
6 Hepatic Flexure



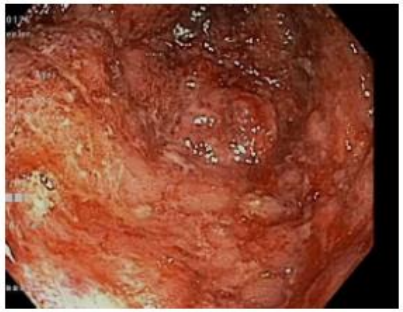
7 Transverse Colon



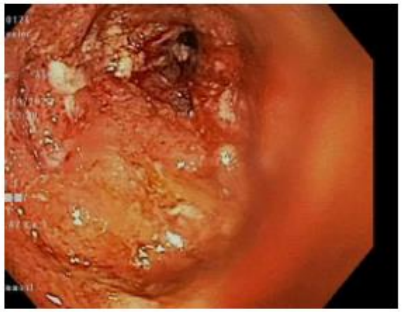
8 Splenic Flexure



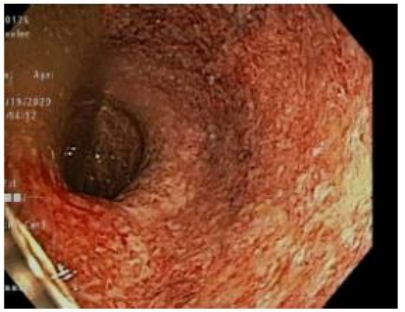
9 Descending Colon



10 Descending Colon

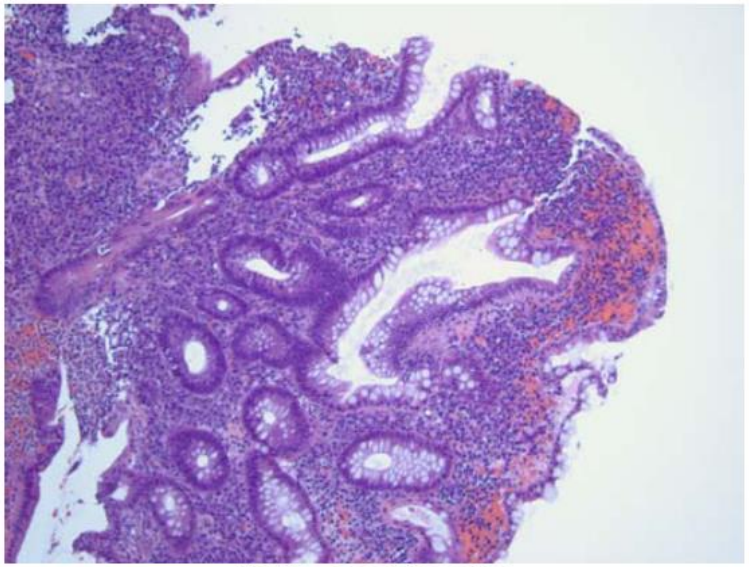


11 Rectosigmoid Junction



12 Rectum

Case Study – Pathology Findings



Part A - ascending colon

DIAGNOSIS

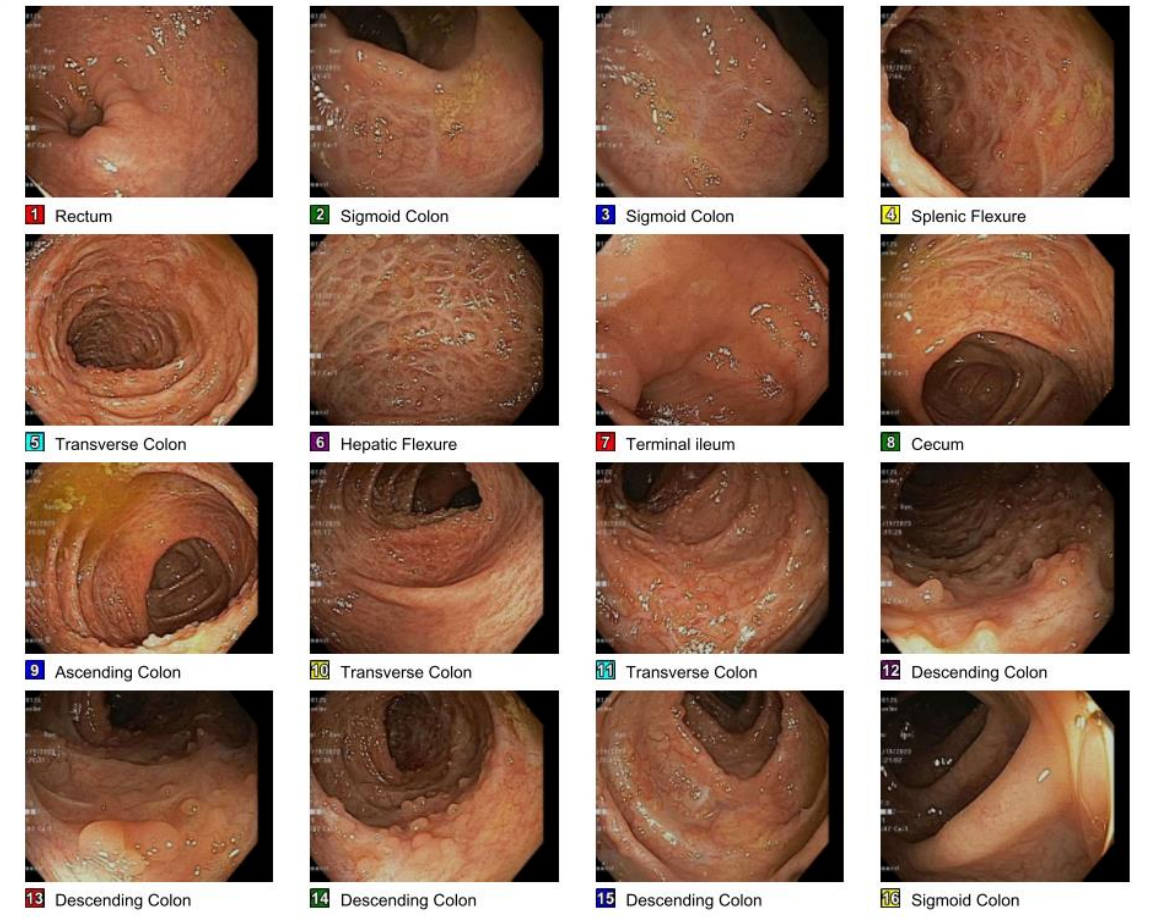
A. ACENDING COLON, BIOPSY:
MARKED CHRONIC ACTIVE COLITIS WITH ULCER, NEGATIVE FOR DYSPLASIA.

B. SIGMOID COLON, BIOPSY:
CHRONIC ACTIVE COLITIS WITH EROSION, NEGATIVE FOR DYSPLASIA.

Case Study

- Infliximab started 3 days after colonoscopy at 10mg/kg (1000mg), plan for 0, 2, 6 weeks then q8 weeks
- OV 2 days after first Infliximab infusion, already improvement in sx. Mesalamine supp DC’d. Prednisone kept at 60mg x 1 week, then decreased to 40mg with 10mg weekly taper dose
- OV 2 weeks later, after 2nd Infliximab infusion, feels significantly better, feels like a "whole new person". Denies abdominal discomfort. He has 3-4 formed stools daily
- We gave him a work excuse x 3 weeks

Case Study – Repeat Colon 10/2020



Pseudopolyps, sigmoid colon, descending colon, transverse colon, ascending colon, cecum, scar at the rectosigmoid colon, inactive (mayo score is 0) ulcerative colitis in remission.

Fast Forward – May 2021 Visit

- Patient returns for routine follow-up.
- Maintained on Infliximab 10 mg/kg every 8 weeks, 1000 mg. He is also on Imuran 100 mg by mouth daily (latter to be discontinued June 2021).
- Denies colitis symptoms. He has 1 formed stool daily with no blood.
- Plan is to repeat colon 2 years from previous (10/2022).

IBD Pre-Treatment Evaluation

Baseline labs:	• CBC • CMP • Fecal calprotectin • CRP, ESR
Disease activity:	• Clinical assessments • Cross-sectional imaging • Endoscopic evaluation • Perianal disease
Medication activity:	• TPMT enzyme activity
Infectious workup:	• Clostridium difficile • Cytomegalovirus infection
Exposure workup:	• Hepatitis B testing • TB testing: Quantiferon Gold or PPD • CXR
Vaccinations:	• MMR, Varicella exposure/vaccination status • Influenza/Pneumonia
IBD medication hx:	• Responder/ non-responder • Adherence • Adverse effects of therapy

Moscandrew et al. *Inflamm Bowel Dis*. 2009; 15:1399-1409.

Collection of Biologics Etc. For Moderate to Severe Disease

Anti-TNF	Anti-integrin	Anti-interleukins	+JAK	+S1P1/PDE4	Immuno-modulators
Adalimumab (Humira) & Biosims (Amjevita, Cyltezo)	Natalizumab (Tysabri) α4β1	Ustekinumab (Stelara) IL 12-23	Tofacitinib (Xeljanz)	Ozanimod (Zeposia) S1P1	Azathioprine (Imuran, Azasan)
Certolizumab (Cimzia)	Vedolizumab (Entyvio) α4β7	* Risankizumab (Skyrizi) Selective IL-23	* Filgotinib Selective Jak-1	* Apremalist (Otezla) PDE4	6-mercaptopurine (6MP, Purinethol)
Golimumab (Simponi)	* Etrolizumab αєβ7	* Mirikizumab Selective IL-23	* Upadacitinib (Rinvoq)	* Etrasimod Selective S1P1	Methotrexate
Infliximab (Remicade) & Biosims (Renflexis, Inflectra, IXIFI)	* Abrilumab α4β7	* Guselkumab (Tremfya) Selective IL-23	* Peficitinib	* Laquinimod Inhibit APC and T cells	Cyclosporine (Sandimmune, Neoral)
	* Ontamalimab α4β7	* Brazikumab Selective IL-23			Tacrolimus (Prograf)
	* AJM 300 & PTG-100 (ORAL)	* PF-04236921 IL-6		*20-30% of patients are primary non-responders	30% of patients become refractory due to secondary loss of response

*Emerging in pipeline; +Small molecules.

Helio gastroenterology. December 2020. Emerging Therapies in IBD; www.crohnscolitisfoundation.org; Lamb C et al. *Journal of Crohns and Colitis.* V12, Issue suppl_2 Aug 2018, pp S653-S668; Sabino et al. *Therapeutic Advances in Gastroenterology.* New biologics and small molecules in IBD: an update. 2019. Vol 12: 1-4.

Anti-TNFs

- Options to **Inject** or **Infuse**

- Adalimumab, biosims
- Certulizumab
- Golimumab
- Infliximab, biosims

Various Indications

Efficacy

CD, UC, RA, PsA, HS, Uveitis, JRA

Safety Profile

Infection, Malignancy, PSA-rxn, SLE-rxn, CHF, ABs

Infliximab

Dosing

- CD and UC
- Loading Dose: 5mg/kg IV at 0, 2, 6 weeks
- Maintenance Dose: 5mg/kg IV starting at week 14 every 8 weeks
- Loss of Response: Increase to 10mg/kg or decrease dosing interval

Safety Highlights

- Increased risk of serious infections leading to hospitalization or death, including TB, sepsis, fungal infections, opportunistic infections. Stop tx if infection.
- Test for latent TB; if positive, start treatment for TB prior to starting REMICADE. Monitor all patients for active TB during treatment, even if initial latent TB test is negative.
- Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with tumor necrosis factor (TNF) blockers, including REMICADE.
- Postmarketing cases of fatal hepatosplenic T-cell lymphoma have been reported in patients treated with TNF blockers including REMICADE. Almost all had received azathioprine or 6-MP concomitantly with a TNF blocker at or prior to diagnosis. The majority of REMICADE cases were reported in patients with Crohn's disease or ulcerative colitis, most of whom were adolescent or young adult males.

Remicade (Prescribing information), Janssen 2020.

Adalimumab

Dosing

- CD and UC
- Now citrate free
- Loading Dose: Day 1- 80mg x 2 (160mg) SQ (syringe or pen), Day 15- 80mg SQ
- Maintenance Dose: 40mg SQ EOW starting at week 4
- Loss of Response: Increase to weekly dosing

Safety Highlights

- Increased risk of serious infections leading to hospitalization or death, including TB, sepsis, fungal and opportunistic infections. Stop tx if infection.
- Perform test for latent TB; if positive, start treatment for TB prior to starting HUMIRA. Monitor all patients for active TB during treatment, even if initial latent TB test is negative.
- Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers including HUMIRA.
- Post-marketing cases of hepatosplenic T-cell lymphoma, a rare type of T-cell lymphoma, have occurred in adolescent and young adults with inflammatory bowel disease treated with TNF blockers including HUMIRA.

Humira (Prescribing information), Abbvie 2021.

Certulizumab Pegol

Dosing

- CD
- Loading Dose: 400mg SQ week 0, 2
- Maintenance Dose: 400mg SQ monthly starting at week 4
- Loss of Response: Give an extra dose of 400mg SQ 2 weeks after last dose or increase to 400mg SQ every 2 weeks

Safety Highlights

- Increased risk of serious infections leading to hospitalization or death including TB, fungal and opportunistic infections. Stop tx if infection.
- Perform test for latent TB; if positive, start treatment for TB prior to starting CIMZIA. Monitor all patients for active TB during treatment, even if initial latent TB test is negative.
- Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers, of which CIMZIA is a member. CIMZIA is not indicated for use in pediatric patients.

Cimzia (Prescribing information), UCB 2019.

Golimumab

Dosing

- UC
- Loading Dose: 200mg SQ at week 0, 100mg SQ at week 2 (syringe or pen)
- Maintenance Dose: 100mg SQ every 4 weeks starting at week 4
- Loss of Response: Dose increase to 100mg SQ every 2 weeks

Safety Highlights

- Serious infections leading to hospitalization or death including TB, sepsis, invasive fungal and opportunistic infections have occurred in patients receiving SIMPONI. Stop tx if infection develops.
- Perform test for latent TB; if positive, start treatment for TB prior to starting SIMPONI. Monitor all patients for active TB during treatment, even if initial latent TB test is negative.
- Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers, of which SIMPONI is a member.

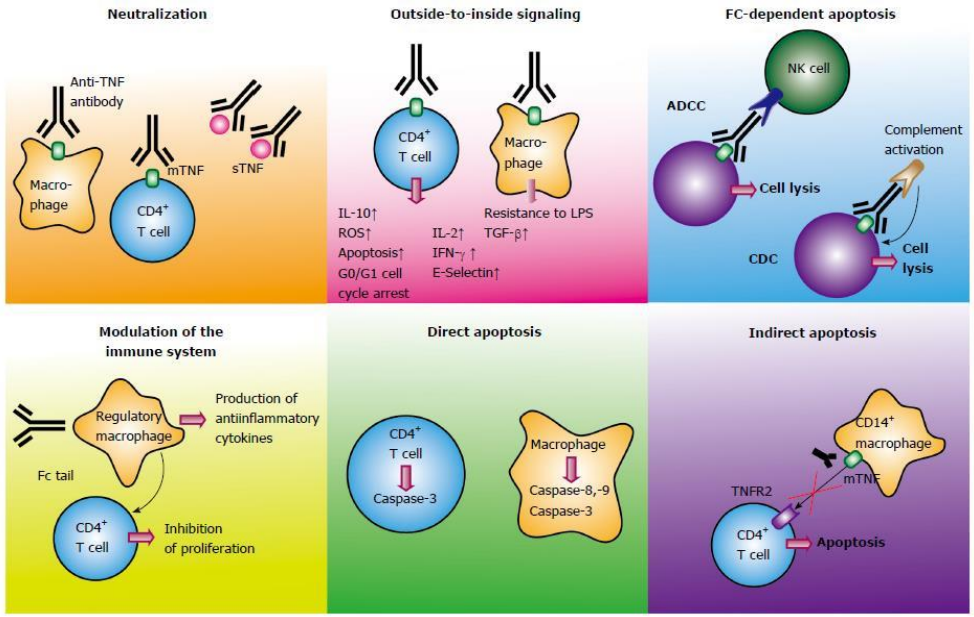
Simponi (Prescribing information), Janssen 2018.

Safety Profile- Anti-TNFs

- Prior to treatment screen for Hepatitis B and TB, consider annual testing, baseline CXR
- Side effects/ Adverse events:
  - Serious/opportunistic/fungal infections
  - TB
  - Hepatitis B
  - Non-Hodgkin/Hepatosplenic T cell lymphoma
  - Skin cancers
  - Lupus like reactions
  - New or worsening heart failure
  - Peripheral demyelinating disease
  - Infusion/injection site reactions

Comparing Anti-TNFs

- Head to head studies are lacking
- Many retrospective studies
- Why do some fail?
  - Inadequate drug on board?
  - How often should levels be drawn?
  - Should this be proactive or retroactive?
  - What are the target levels?
  - Antidrug Antibodies?
  - Should immunosuppressants be used in conjunction to decrease immunogenicity and for how long?
  - Adherence to therapy?
  - Infection?



Billmeier U, Dieterich W, Neurath MF, Atreya R. Molecular mechanism of action of anti-tumor necrosis factor antibodies in inflammatory bowel diseases. *World J Gastroenterol*. Nov 14, 2016; 22(42): 9300-9313.

Factors That Influence the Pharmacokinetics of Biologics

	Impact on TNF antagonist PK
Presence of ADAs	Decreases drug concentration Increases clearance Worse clinical outcomes
Concomitant use of immunosuppressants	Reduces ADA formation Increases drug concentration Decreases drug clearance Better clinical outcomes
Low serum albumin concentration	Increases drug clearance Worse clinical outcome
High baseline CRP concentration	Increases drug clearance
High baseline TNF concentration	May decrease drug concentration by increasing clearance
High body size	May increase drug clearance
Sex	Males have higher clearance

Ordas I et al. *Clinical Gastroenterology Hepatology.* 2012; 10:1079-1087

Anti-TNFs in a Nutshell

- Work quickly, sometimes after just one dose
- Dosed every 2 weeks- 2 months by IV or SQ
- Long-term safety
  - Increased risk of melanoma (with added thioprines) and NHL
  - Lymphoma risk not supported by data and no increased risk of solid malignancies
  - Increased risk of infections
- May become allergic or ineffective if stopped and then resumed later
- TDM-based dose adjustments
- Treat EIMs
- High immunogenecity and need for concomitant immunosuppression
- Understanding difference between class effect non-response and individual drug effect (swapping vs cycling)

Sandborn W et al. *Gastroenterology & Hepatology*. Vol 17, Issue 4, Suppl 4, April 2021.

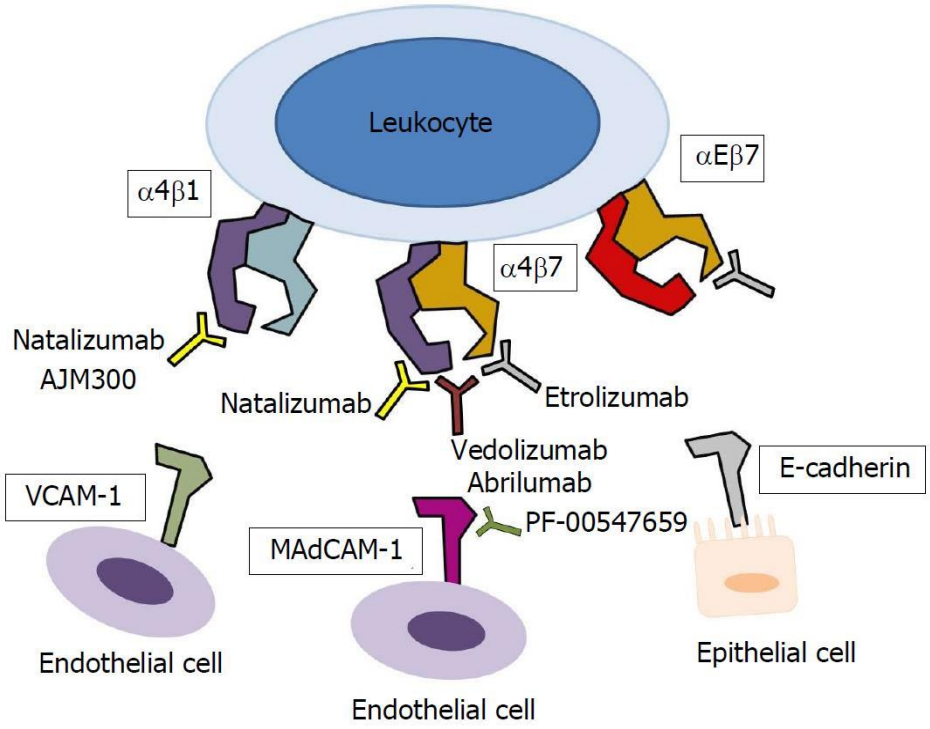
Combination Therapy

- Anti-TNF biologic + immunomodulator yields best outcomes
  - Highest response rates (especially in UC)
  - Lowest rates of neutralizing ab's
  - Lowest rates of loss of response

  → BUT
  - Slightly higher rates of infection
  - Higher rates of lymphoma especially with thioprines
- Once remission is achieved may try to taper off thioprine

Anti-Integrins

- Organ specific
- Excellent safety profile
- Low immunogenicity
- Some studies show efficacy in fistulizing disease
- CD and UC



Park SC, Jeen YT. Anti-integrin therapy for inflammatory bowel disease. *World J Gastroenterol*. May 7, 2018; 24(17): 1868-1880.

Natalizumab

Dosing

- CD
- Loading Dose: None
- Maintenance Dose: 300mg IV every 4 weeks
- Loss of Response: DC after 12 weeks if no therapeutic benefit or 6 months if concomitant steroids cannot be discontinued

Safety Highlights

- TYSABRI increases the risk of progressive multifocal leukoencephalopathy, an opportunistic viral infection of the brain that usually leads to death or severe disability
- Risk factors for the development of PML include the presence of anti-JCV antibodies, duration of therapy, and prior use of immunosuppressants. These factors should be considered in the context of expected benefit when initiating and continuing treatment with TYSABRI.
- Monitor patients, and withhold TYSABRI immediately at the first sign or symptom suggestive of PML.
- Because of the risk of PML, TYSABRI is available only through a restricted distribution program called the TOUCH® Prescribing Program.

Tysabri (Prescribing information), Biogen 2020.

Vedolizumab

Dosing

- CD and UC
- Loading Dose: 300mg IV weeks 0, 2, 6
- Maintenance Dose: 300mg IV every 8 weeks starting at week 14
- Loss of Response: 300mg IV every 4 weeks. For refractory disease, DC if no response by week 14

Safety Highlights

- Infusion-Related Reactions and Hypersensitivity Reactions: Discontinue ENTYVIO and initiate appropriate treatment if serious reactions occur.
- Infections: Treatment with ENTYVIO is not recommended in patients with active, severe infections until the infections are controlled. Consider withholding ENTYVIO in patients who develop a severe infection while on treatment with ENTYVIO.
- Progressive Multifocal Leukoencephalopathy: Although unlikely, a risk of PML cannot be ruled out. Monitor patients for any new or worsening neurological signs or symptoms.

Entyvio (Prescribing information), Takeda 2021.

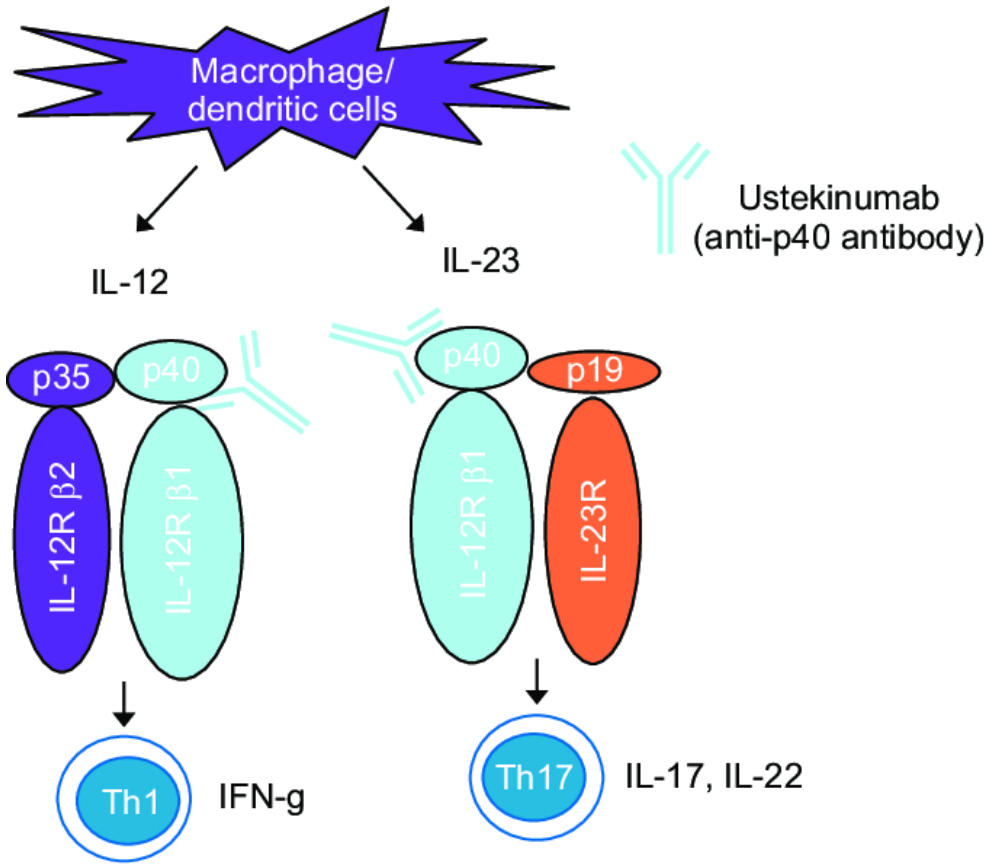
Anti-Integrins in a Nutshell

- ***For Vedolizimab***
- Screen for TB and HBV for insurance purposes
  - Full onset of action may take 2-3 months
  - May need to “bridge” sick patients with a short acting agent for the first few weeks or months
  - Gut specific, may not be as effective for EIMs
  - No known safety risk unless allergic or intolerant
  - Low immunogenicity
  - Live vaccines
  - ***No significant risk of malignancy or opportunistic infections***
  - Increase to monthly infusions if patient has loss of response or suboptimal response
- ***For Natulizunab***
  - Crosses the blood brain barrier, **risk for PML**, must monitor JC virus

Sandborn W. et al. *Gastroenterology & Hepatology*. Vol 17, Issue 4, Suppl 4, April 2021.

Anti-Interleukins

- Both CD and UC
- Low immunogenicity
- Injection after loading IV dose
- Favorable safety profile
- Durable



Hiroshi N. *Gut and Liver*. Published online March 12, 2019; Optimizing the Use of Current Treatments and Emerging Therapeutic Approaches to Achieve Therapeutic Success in Patients with Inflammatory Bowel Disease.

Ustekinumab

Dosing

- Loading:

  <55kg, 260mg IV x 1

  55-85kg, 390mg IV x 1

  >85kg, 520 IV x 1

- Maintenance: 90mg SQ every 8 weeks starting after initial infusion
- Loss of Response: Dose escalation to 90mg SQ every 4 weeks

Safety Highlights

- Infections: Serious infections have occurred. Do not start STELARA during any clinically important active infection. Stop tx if infection develops.
- Theoretical Risk for Particular Infections: Serious infections from mycobacteria, salmonella and BCG vaccinations have been reported in patients genetically deficient in IL-12/IL-23. Diagnostic tests for these infections should be considered as dictated by clinical circumstances.
- Evaluate patients for TB prior to initiating treatment with STELARA. Initiate treatment of latent TB before administering STELARA.
- Malignancies: STELARA may increase risk of malignancy. The safety of STELARA in patients with a history of or a known malignancy has not been evaluated.
- Hypersensitivity Reactions: Anaphylaxis or other clinically significant hypersensitivity reactions may occur.
- Posterior Reversible Encephalopathy Syndrome: If PRES is suspected, treat promptly and discontinue STELARA.
- Noninfectious Pneumonia: Cases of interstitial pneumonia, eosinophilic pneumonia and cryptogenic organizing pneumonia have been reported during post-approval use of STELARA. If diagnosis is confirmed, discontinue STELARA and institute appropriate treatment.

Stelara (Prescribing information), Janssen 2020.

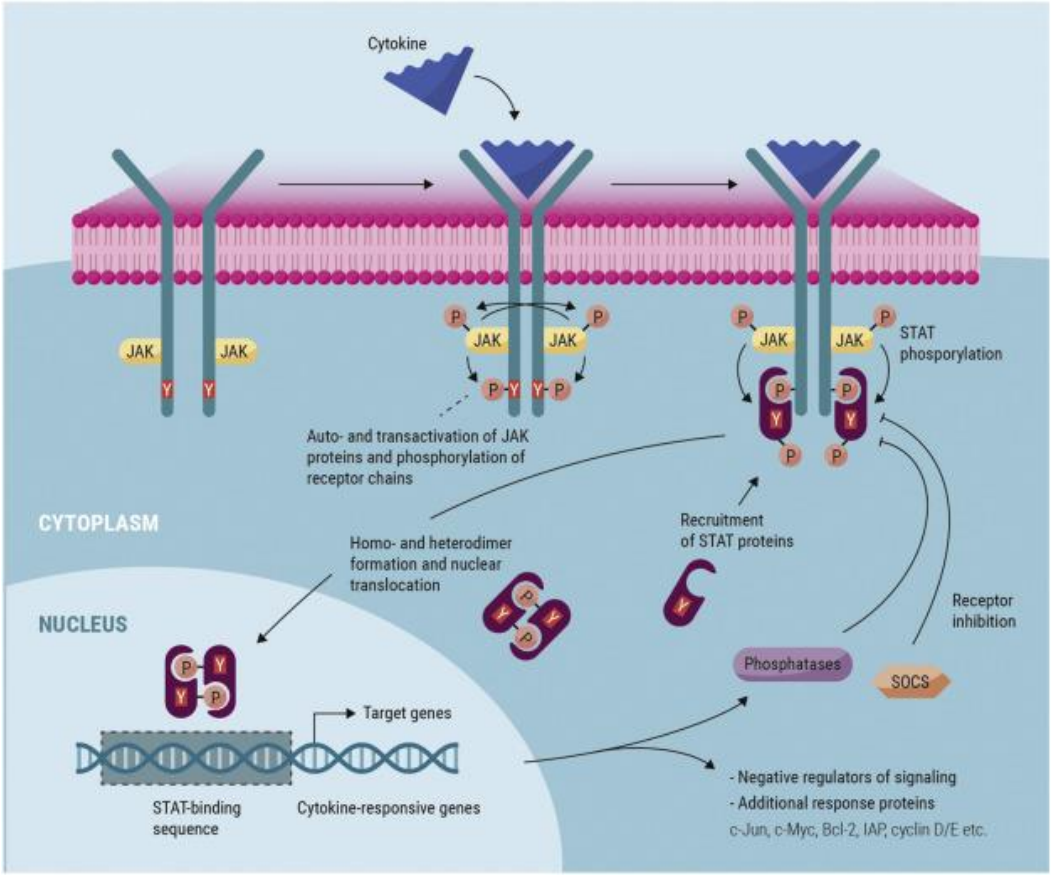
Anti-Interleukins in a Nutshell

- Screen for TB and HBV prior to treatment
- Two separate insurance approvals required
  - 1 for IV and 1 for SQ injections
- Not clear if immunosuppressants provide any benefit
- Attractive for patients with psoriasis or who get psoriasis rash from anti-TNFs not easily treated with topical dermatologic agents
- Not known to increase risk lymphoma or other cancers
  - ? Increased risk of squamous cell skin cancer in susceptible patients
- Infection risks less than that from anti-TNFs, excellent safety profile
- Low immunogenicity
- **NO** black box warnings

Sandborn W et al. *Gastroenterology & Hepatology*. Vol 17, Issue 4, Suppl 4, April 2021.

JAK/STAT

- UC
- Small molecule (not a biologic)
- No immunogenicity
- Not bound to albumin
- Oral
- Multi-inhibition of pre-inflammatory signaling
- Check lipid panel after initiation



Soendergaard F et al. *Pharmacology and Therapeutics*. December 2018. Targeting JAK-STAT signal transduction in IBD.

Tofacitinib

Dosing

- Loading: 10mg PO BID or 22mg XR PO daily x 8 weeks
- Maintenance: 5mg PO BID or 11mg XR PO daily (reassess with objective measures- CRP, fecal cal, flex sig) before decreasing to 5mg BID dose
- Loss of Response: May continue 10mg PO BID or 22mg XR PO daily for up to 16 weeks total if initial response lost; DC if no benefit after this time
- Use lowest effective dose to maintain response
- ½ the daily dose if moderate to severe renal or hepatic impairment

Safety Highlights

- Serious infections leading to hospitalization or death, including tuberculosis and bacterial, invasive fungal, viral, and other opportunistic infections, have occurred; stop and tx infection if occurs
- Check TB prior to start
- Thrombosis, including pulmonary embolism, deep venous thrombosis and arterial thrombosis have occurred, use lowest dose
- Lymphoma and other malignancies have been observed

Xeljanz (Prescribing information), Pfizer 2020.

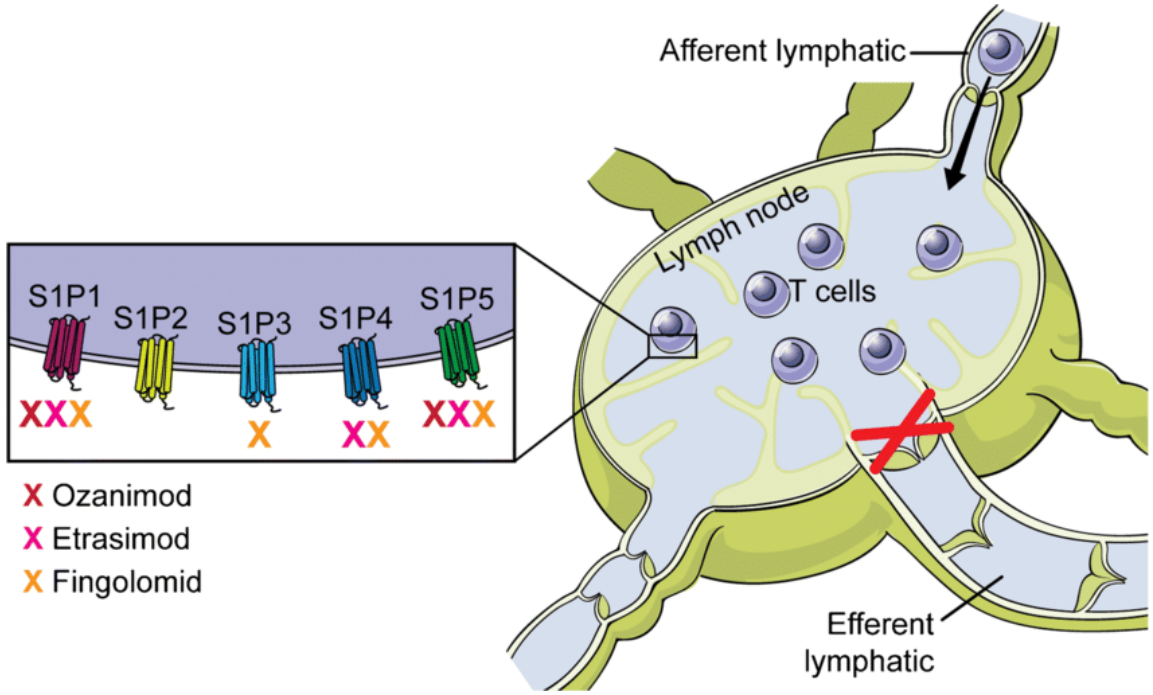
Jak Inhibitors in a Nutshell

- Quick response in some individuals (days) with quick wash-out
- Oral dosing
- No immunogenicity
- Stable PK
- Not recommended in combination with biologics or immunomodulators
- Not to be used in pregnancy
- Mild elevation in cholesterol (10-15%)
- Higher risk of zoster reactivation (5%)
  - Give recombinant shingles vaccine
- Increased risk of pulmonary embolism/DVT
- Monitor CBCD/CMP/Lipids on therapy, cytopenias may occur
- Unknown risk of lymphoma or other cancers
- Not approved for biologic naïve patients

Sandborn W et al. *Gastroenterology & Hepatology*. Vol 17, Issue 4, Suppl 4, April 2021.

S1P1

- UC
- Small molecule
- Oral



Ozanimod

Dosing

- Loading: 0.23 mg PO daily x 4 days, then 0.46 mg PO daily x 3 days
- Maintenance: 0.92 mg PO daily starting at day 8
- Loss of Response: Restart titration if dose missed w/in first 2 weeks of tx; if dose is missed after 1st 2 weeks of tx, continue tx as planned

Safety Highlights

- Contraindication if in the last 6 months, experienced MI, angina, stroke, TIA, HF, Mobitz type II second-degree or third degree AV block, SSS, OSA
- May increase risk of infections, don't give if active infection, check CBC 1st, monitor
- May decrease HR, check EKG, cardiac eval, monitor BP, may increase
- Monitor LFTs
- Don't use in pregnancy

Zeposia (Prescribing information), Bristol Myers Squibb, 2021.

Immunomodulators

- MTX
  - Maintanence therapy for Crohns
  - Dosing: 7.5-25 mg PO/SQ weekly + folic acid 1mg PO daily
  - Side effects: flu-like sx, HA, nausea, malaise
  - Contraindicated in pregnancy (fetal anomalies) and decreased sperm count in men (reversible)
  - Limit ETOH to 1-2 drinks per week (hepatotoxicity)
  - Increased risk of skin cancers

* Tips: SQ has better absorption/ less side effects; premedicate with ondansetron or acetaminophen; helpful in patients with joint pains.

Immunomodulators, Cont'd

- Thiopurines
  - Azathioprine, 6 MP
  - Maintenance of remission in CD and UC
  - Dosing: 1.5-2.5mg/kg/day (25-250mg /day)
  - Check TPMT prior to starting therapy and thiopurine metabolites for monitoring
  - Potential side effects include: pancreatitis, N/V, hepatotoxicity, infection, myelosuppression
  - Risk of lymphomas: Non-Hodgkins (4/10,000) and non-melanoma skin cancers

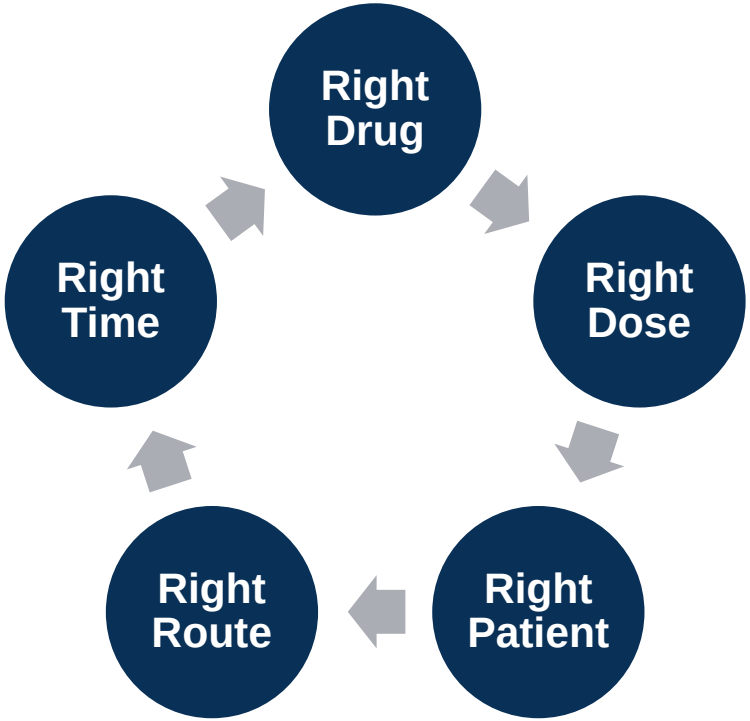
* Tips: Discuss potential risks; requires weeks to months to see full effect; do not use in elderly / non-compliant pts; dose optimization (goal: 6TG >235, 6MMP <5700).

Immunomodulators in a Nutshell

- May be helpful by themselves or with another agent in the following circumstances:
  - Nonresponse or intolerance to 5ASAs, abx or steroids
  - Steroid dependent disease
  - Perianal disease not responding to abx
  - Fistulas
  - Bolster/optimize effect of biologics and prevent ADA
  - Prevent recurrence after surgery
- May take 3-6 months to see improvement, so may need steroids for faster response
- Need to monitor labs during treatment, including CBC/LFTs/Amylase
- Avoid in pregnancy

Future of IBD Treatment

Personalized Medicine



- Treatment derived from patient genetic profile
- Using biomarkers that predict risk for disease and response to treatment as a treatment guide to patient care
- Patient involvement in decision making

Flamant et al. *Therapeutic Advances in Gastroenterology.* 2018. Vol. 11: 1-15.

What Is This “Immunogenicity”

- Immunogenicity is recognized as a leading contributor to the loss of response to biologic therapies; as biologic agents are large, complex proteins, they trigger the formation of anti-drug antibodies (ADAs) specific to the agent administered
- It is recommended that patients who develop ADAs to a biologic therapy, with a consequent loss of response, should switch to a different agent with either the same or a different mechanism of action
- Giving biologic therapies in combination with concomitant immunosuppressive agents has been shown in several studies to reduce the development of ADAs

Severine et al. *Ther Adv Gastroenterology*. 2018;11:1-13.

Therapeutic Drug Monitoring

- Used to check the drug trough concentration and assess for the presence of anti-drug antibodies
- Can be performed at any point of therapy in induction or maintenance
- Can be routine proactive when patient in remission or reactive during symptoms
- Primary nonresponse to anti-TNF therapy occurs in approximately 1/3 of patients
- Development of anti-drug antibodies correlates with inadequate drug levels and loss of response
- Measurable drug level at trough associated with improved response outcomes
- Reduce adverse events associated with supra-therapeutic drug concentrations
- Cost effective

Feuerstein J et al. *Gastroenterology*. 2017 (153); 827-834; Flamant et al. *Therapeutic Advances in Gastroenterology*. 2018. Vol. 11: 1-15.

Emerging Diagnostics

- Pharmacogenomics – drug-gene testing
- Find predictors of clearing the disease
- Need for identifying biomarkers predictive of response to individual therapies, facilitate optimal positioning of therapies
- Optimize strategies to increase the efficacy of drugs ie. finding biomarkers of response to a drug and/or combining drugs to increase likelihood of healing and of achieving disease clearance
- Treat to target
  - This treat-to-target approach has been associated with improved disease outcomes such as diminished bowel damage, surgery and hospitalizations
  - Many patients with IBD require biologic therapy to achieve and maintain clinical and endoscopic remission, and antitumor necrosis factor antibodies remain the first-line biologic therapy in most areas of the world
  - Unfortunately, up to 1/3 of patients receiving this treatment are primary non-responders, and some patients that show an initial response can also lose response over time
  - TDM has been suggested as a useful tool to manage treatment, including monitoring for dose escalation, de-escalation or to switch treatment
- Apheresis – tx developed in Japan- based on local immunomodulation achieved by removing leukocyte (granulocytes, monocytes, and activated lymphocytes) from the peripheral blood. With no additive drugs, this appears to be natural biologic therapy and may be a groundbreaking treatment method
- FMT, stem cell therapy emerging…

Argollo et al. *Nat RevGastroenterol Hepatol.* Sept 2020; Flamant et al. *Therapeutic Advances in Gastroenterology*. 2018. Vol. 11: 1-15; Nakasa, H. *Gut and Liver*. Optimizing the Use of Current Therapies and Emerging Therapeutic Approaches to Achieve Therapeutic Success in Patients with IBD. March, 2019; Colombel, J. *Gastroenterology & Hepatology.* 2021, Vol 17, Issue 5, May.

Don’t Forget the Crohn’s Colitis Foundation!

- Crohnscolitisfoundation.org
  - Professionals
  - For your patients
  - Appeal letters
- Plethera of information including:
  - School/employment accommodations
  - Disability
  - Financial resources
  - Medication dose escalations
  - Prior authorization letters, other testing including fecal calprotectin, etc…(references professional journal articles)

In Summary

- Treat to target
  - Use effective therapies earlier
- Reassess with objective measures (CRP, fecal calpro, flex sig) before starting therapy and 3-6 months later
- Optimize therapies
  - Use drug levels as a guide, adjust as needed
  - Treat the patient!
- Combination therapy most effective
  - Especially in anti-TNFs and if failed other therapies or developed ab
- Recognize non-response and loss of response
- Avoid lapses in treatment

Thank You!


Our usual colonoscopy equipment is down today, so we're going to be using a tapeworm with a GoPro strapped to its head.
Blazek
5-27
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