Inflammatory Bowel Disease

728-655
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Learning Objectives

- Review the clinical presentation of IBD
- Understand the basic principles of management of IBD
- Choose patients to monitor on biologic therapy
- Review risk of infections with IBD therapy

Reading Assignment

Pharmacotherapy. A Pathophysiologic Approach,
11th edition. Chapter 51. Inflammatory Bowel Diseease. Pp 507-527

Read this *two page* synopsis of the 2018 ACG Clinical Guideline: Management of Crohn's Disease in Adults. (posted on Canvas)
Field L, Glick LR, Cifu AS. Diagnosis and management of Crohn disease. JAMA April 10, 2019 E1-2

Abbreviations:
6-TGN =6-thioguanine nucleotide (metabolite of 6MP or AZA)
6-MMP = 6-methylmercaptopurine (metabolite of 6MP or AZA)
IFX= infliximab
Tofa or TOF = tofacitinib
TNF=tumor necrosis factor
AZA= azathioprine
MTX= methotrexate
6MP= 6-mercaptopurine
TMPT=thiopurine methyltransferase; a polymorphic enzyme for the metabolism of AZA/6MP

Study questions
What is the mechanism of action of:
Azathioprine?
Infliximab?
Vedolizumab?

What are the benefits of infliximab therapeutic monitoring?

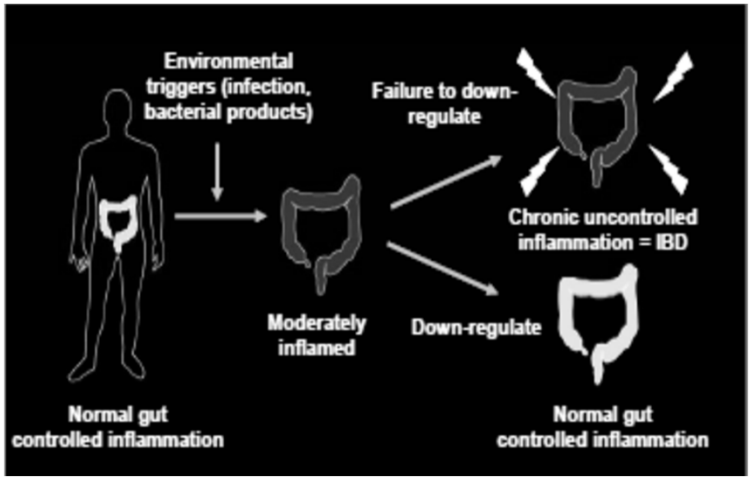
List complications of IBD treatment.

Inflammatory Bowel Disease

- Is NOT
  - An Allergy
  - An immune deficiency
  - Irritable Bowel Syndrome
- Is
  - Inflammatory activated immune system in the intestinal tract
  - Chronic – last a long time (maybe lifetime)
  - Treatable

Working hypothesis

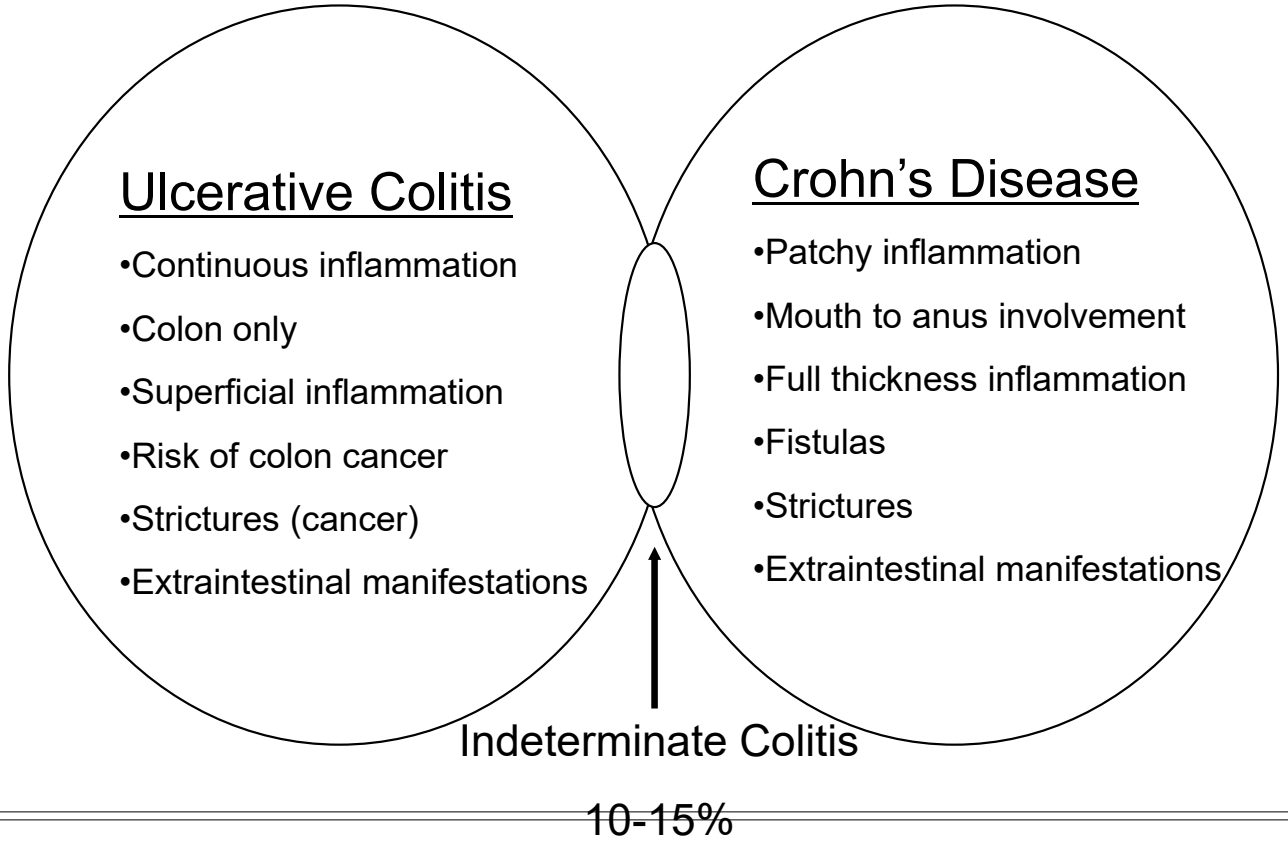
- IBD results from a dysregulated response of the mucosal immune system towards intraluminal antigens of bacterial origin in genetically predisposed individuals



What is IBD?

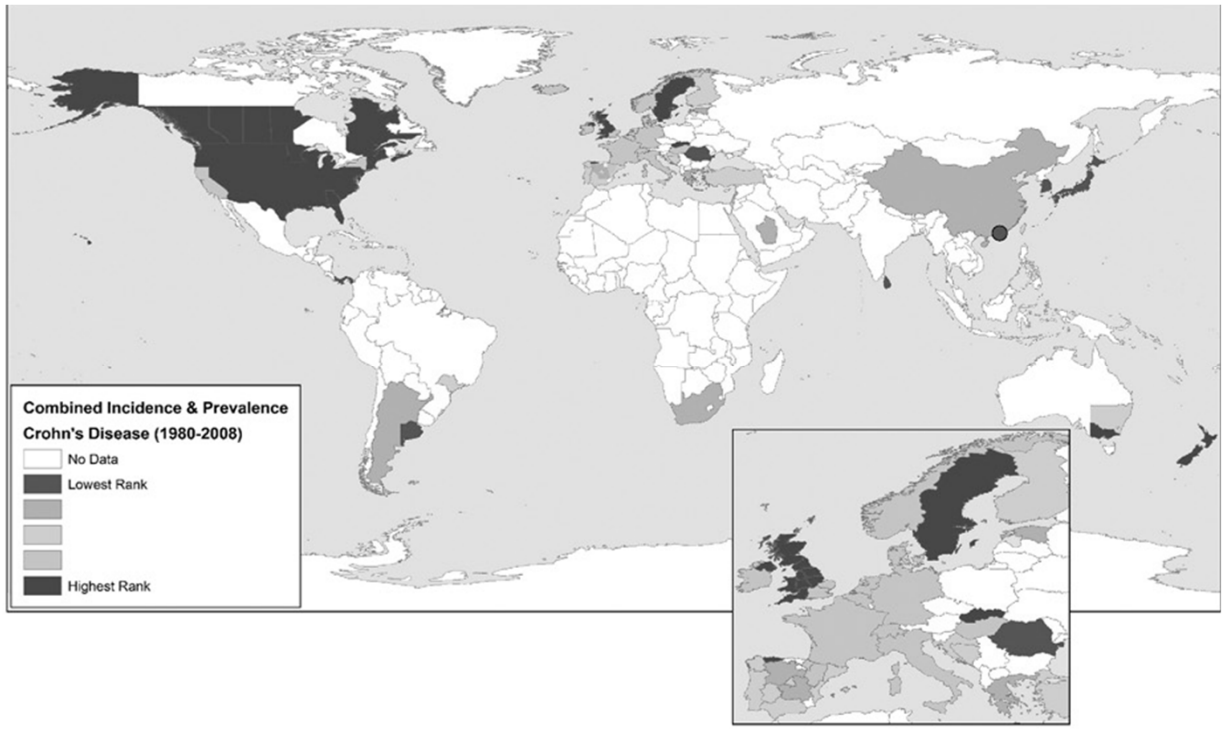
- Chronic inflammatory condition of the GI tract
- Characterized by periods of disease quiescence (remission) and activity (flare)
- 2 main forms:
  - Ulcerative colitis (UC)
  - Crohn's disease (CD)

The Spectrum of IBD



Incidence IBD < 1960

Incidence 1980-2008



Global IBD prevalence, 2015

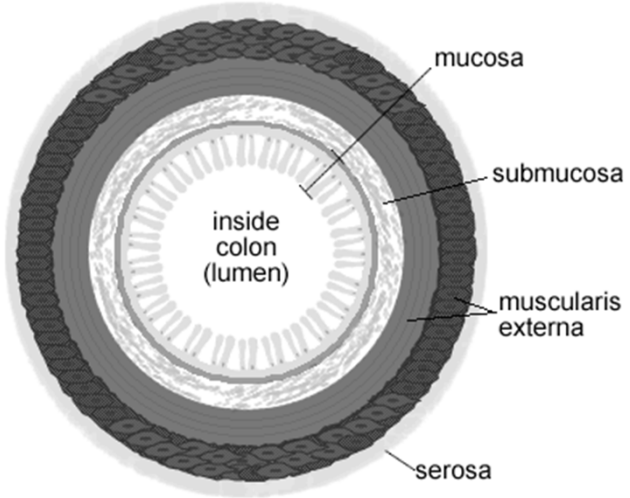
Kaplan, GG, Nature Rev. Gastroenterol Hepatol 2015

Epidemiology of IBD: Incidence and Prevalence

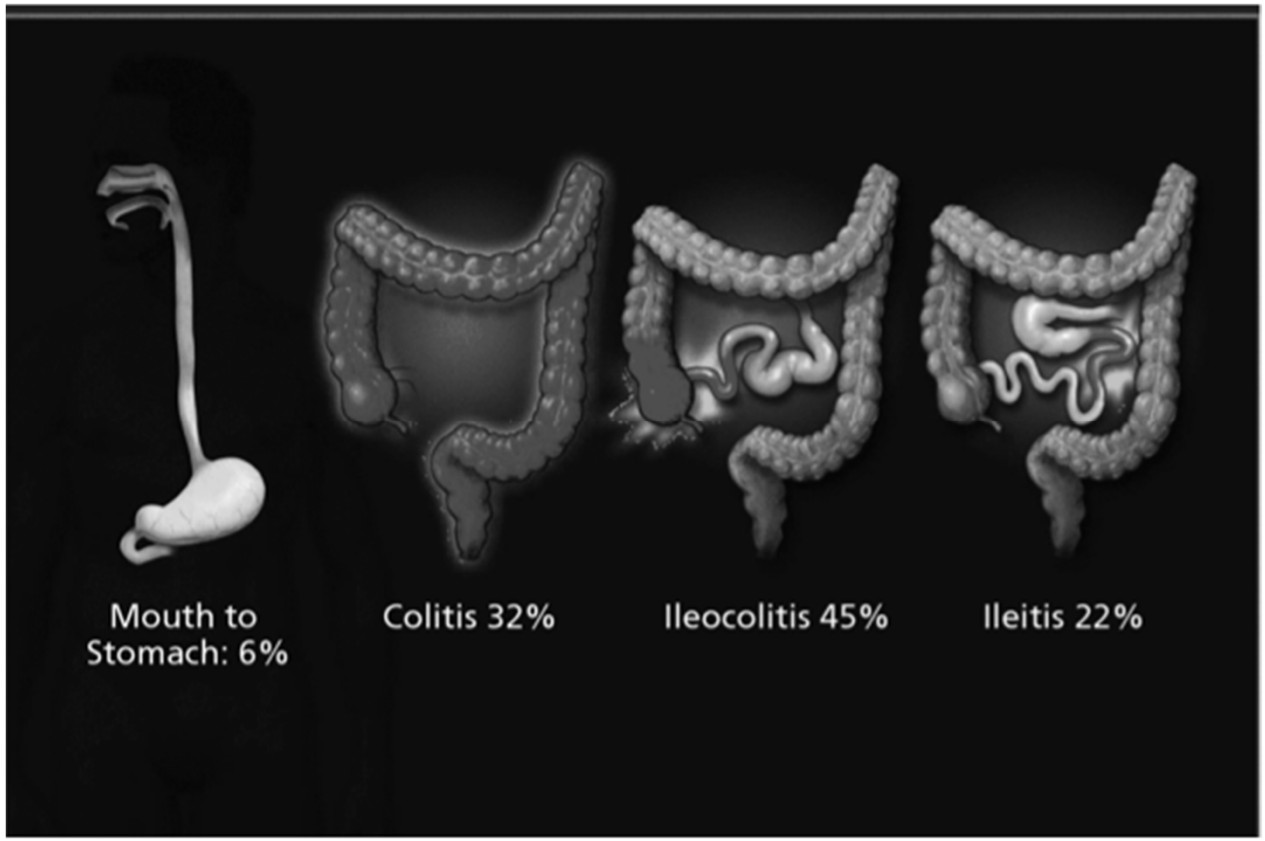
- 1.4 million Americans affected by IBD
  - 70,000 new cases per year
- Worldwide incidence of IBD is on the rise
- Becoming more common in areas where prevalence had been low

Crohn's Disease

- Inflammation extending through all layers of the GI tract (*transmural inflammation*)
- Can involve any part of the GI tract (mouth to anus)
- Inflammation is full-thickness
- Fistulas and strictures occur
- Symptoms depend on extent and severity of disease



Crohn’s disease Extent and location



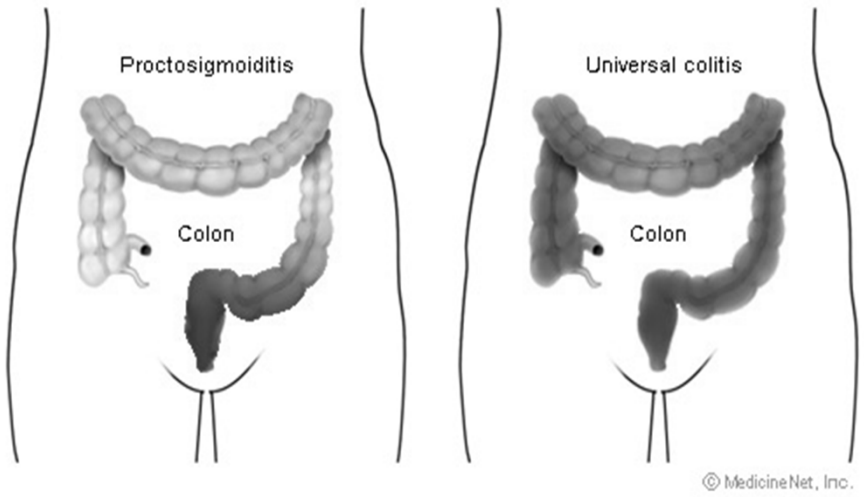
Signs and symptoms: CD

- Abdominal pain
- Diarrhea (usually non-bloody)
- Weight loss
- Fatigue
- Iron deficiency anemia
- Extraintestinal manifestations

Ulcerative colitis

- Inflammation limited to the superficial most layer of the GI tract (mucosa)
- Involves all or part of the colon
- Does not involve other areas of the GI tract

Ulcerative colitis: Extent and location



Proctitis 20%

Left-sided colitis 50%

Pancolitis 30%

Signs and symptoms: UC

- Fecal urgency
- Tenesmus
- Hematochezia
- Abdominal pain
- Fever
- Iron deficiency anemia
- Extraintestinal manifestations

Goals of therapy

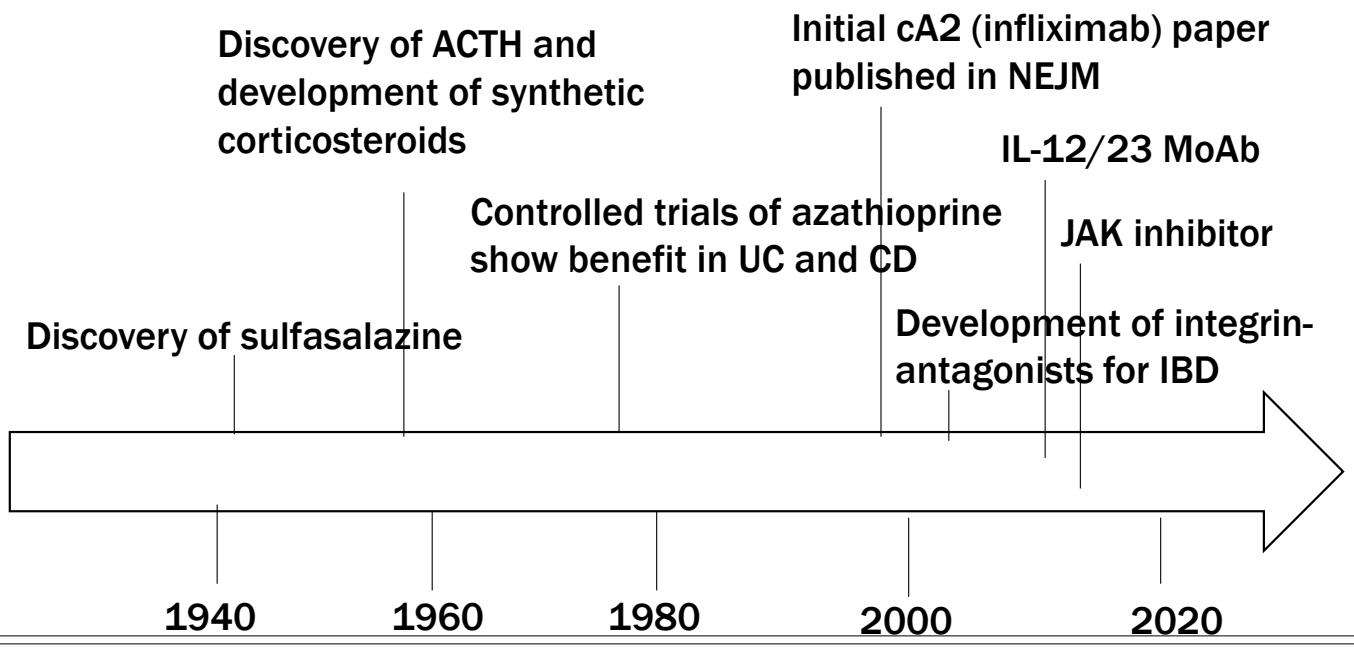
- Induce symptomatic remission
- Maintain steroid-free remission
- Control inflammation
- Enhance quality of life
- Prevent/treat complications of disease
- Avoid short and long term toxicity of therapy

What drug classes are available for treatment?

- Aminosalycilates
- Immunomodulators
- Biologics
  - Anti cytokine agents
  - Anti-adhesion agents
  - JAK inhibitors
- Steroids

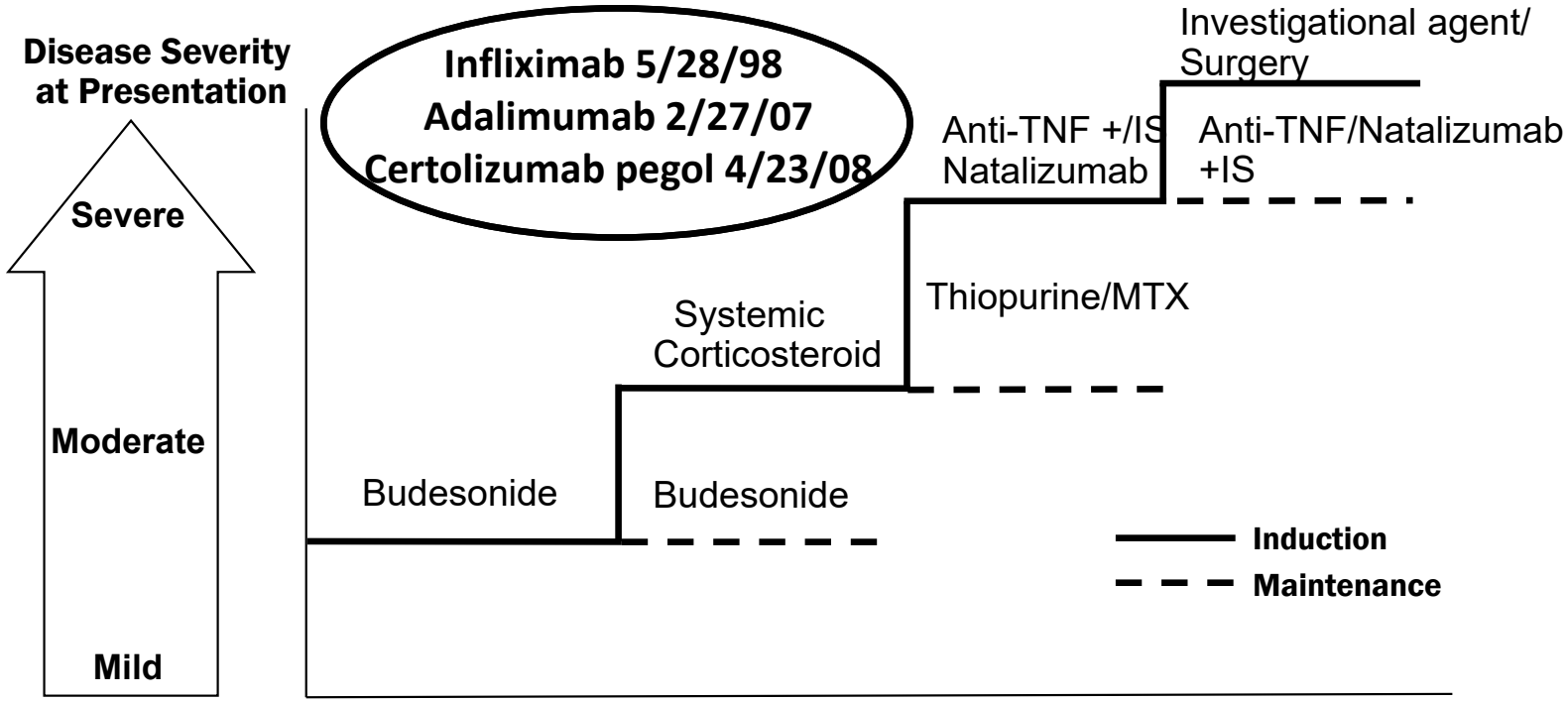
IBD Treatment: The historical perspective

A limited number of time stamps during the past century have marked significant changes in IBD management



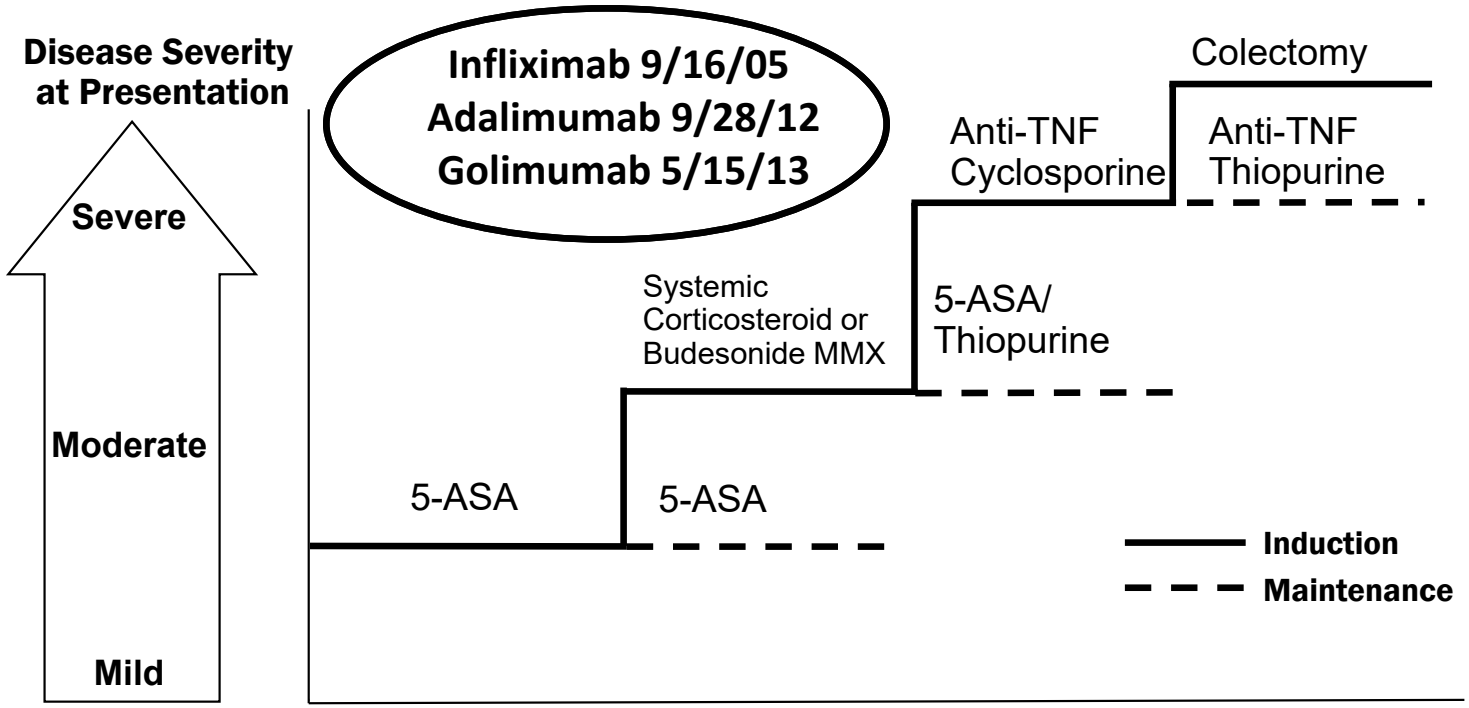
Kirsner JB. Inflamm Bowel Dis 1996;2:73:81

Traditional Step-UP Therapy for CD



Therapy is stepped up according to severity at presentation or failure at prior step

Traditional Step-UP Therapy for UC



Therapy is stepped up according to severity at presentation or failure at prior step

Crohn's disease: High risk for rapid progression to bowel damage and disability

- Early onset < 40 years
- Small bowel involvement
- Perianal disease
- Endoscopic severe lesions
- Prior surgical resection

5- Aminosalicylates

- Small benefit in CD—not recommended
- Effective for induction of remission in UC; generally in 2 to 8 weeks
- No differences in rates of inductions of remission among various preparations
- Once daily as effective as split dosing and better adherence

5-ASA drugs
Balsalazide
Mesalamine
Olsalazine
Sulfasalazine

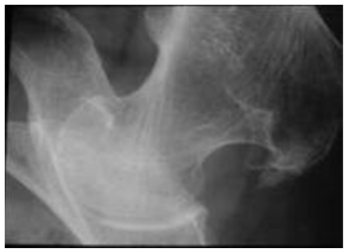
Sandobrn WJ, Et al. Gastroenterology 2009

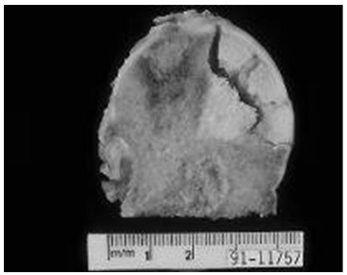
Corticosteroids

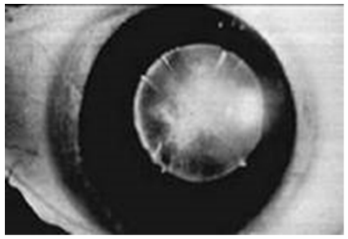
- Indicated for those failing 5ASA, budesonide, moderately severe disease
- Effective for induction of remission, no role in maintenance
- Poor side effect profile
- May be used in combination with an anti-TNF to induce remission in moderate to severe CD
- Doses >60mg/d not more effective
- Effective in 1 to 3 weeks
- Anticipate steroid dependence in ~ 25% of patients

Serious Potential Adverse Effects From Prolonged Corticosteroid Therapy

Adverse effect
Infection
Hypertension
Diabetes
Osteonecrosis
Osteoporosis
Myopathy
Cataracts
Glaucoma
Psychosis





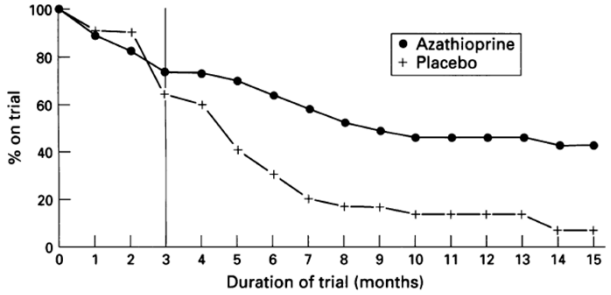


Use of corticosteroids in IBD should *always* have an effective exit strategy.

Lichtenstein GR et al. ACG 2008;Abstract 14
Sandborn WJ. *Can J Gastroenterol*. 2000;14(suppl C):17C-22C

Thiopurines

- Indications
  - Steroid dependence
  - As part of combination therapy with biologics
  - Post operative prophylaxis (CD)
  - Fistulas
- TMPT testing advised before starting
- Dosing
  - Mercaptopurine 1-15.mg/kg
  - Azathioprine 2-2.5mg/kg
- Onset of effect: 8-16 weeks



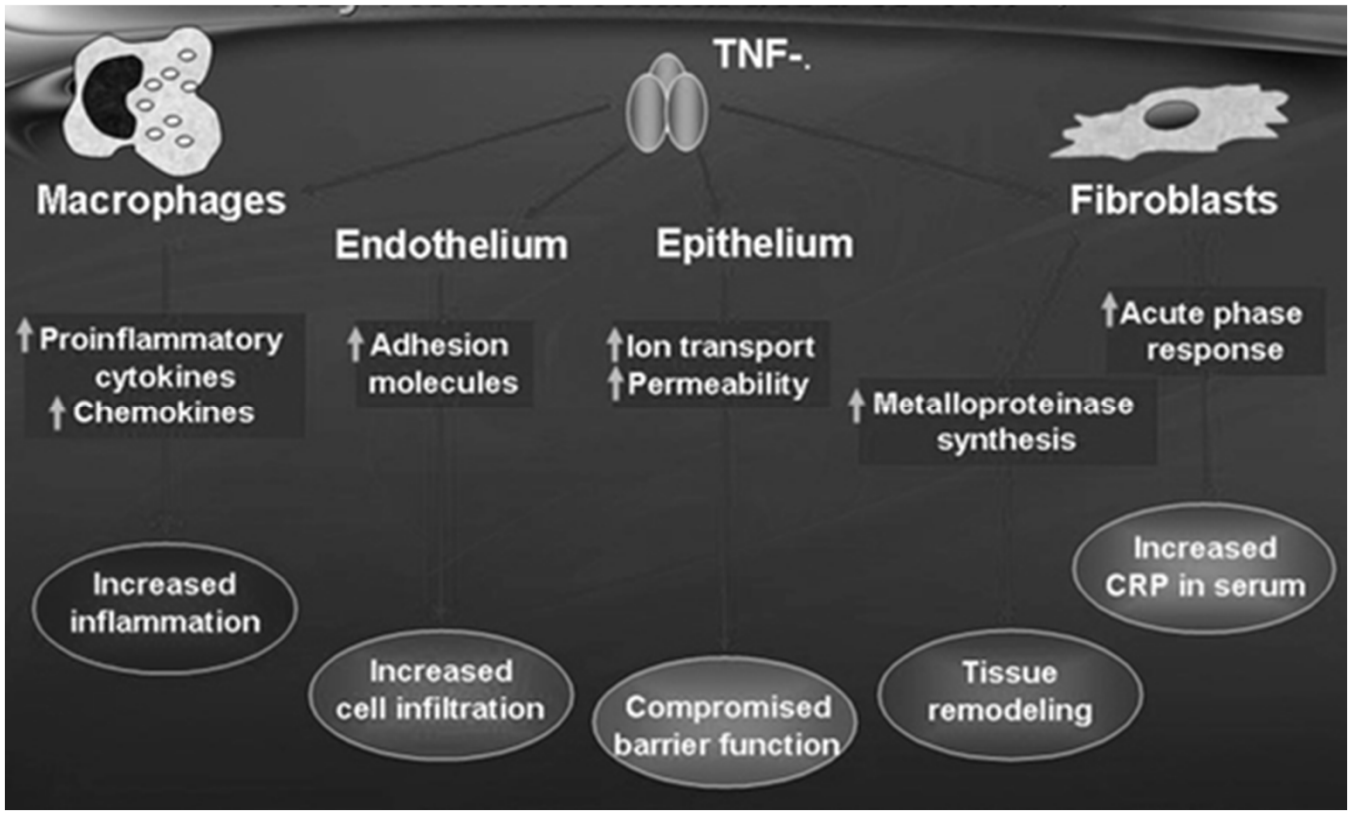
Methotrexate

- Indications (CD; ?UC)
  - Steroid dependence
  - Steroid refractory
  - As part of combination therapy with biologics
- Dosing
  - SC or IM: 25mg weekly
  - PO : 7.5-15mg weekly
- Onset of effect: 8-16 weeks
- Effective contraception needed

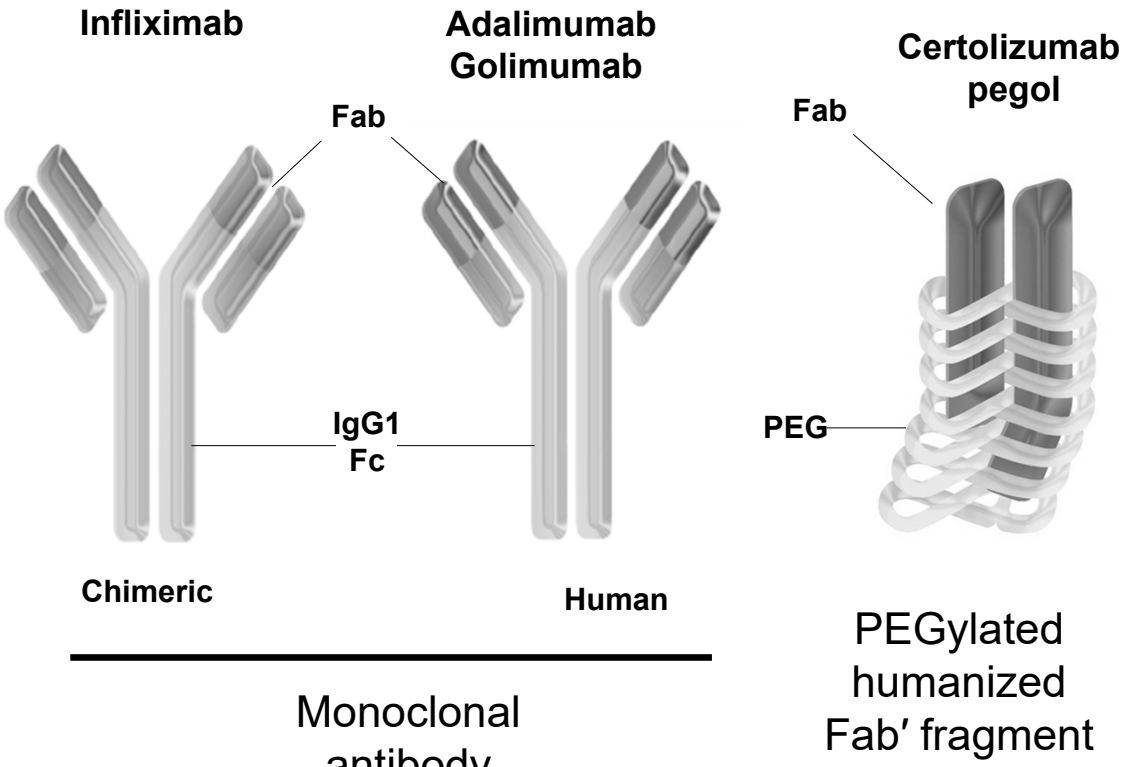
Tumor Necrosis Factor (TNF) alpha

- TNF alpha is know to play a crucial role in pathogenesis of chronic inflammation
- Elevated in IBD, psoriasis, psoriatic arthritis, and rheumatoid arthritis.
- TNF play a critical role in activation of innate and adaptive immune response.

Key Action Attributed To TNF



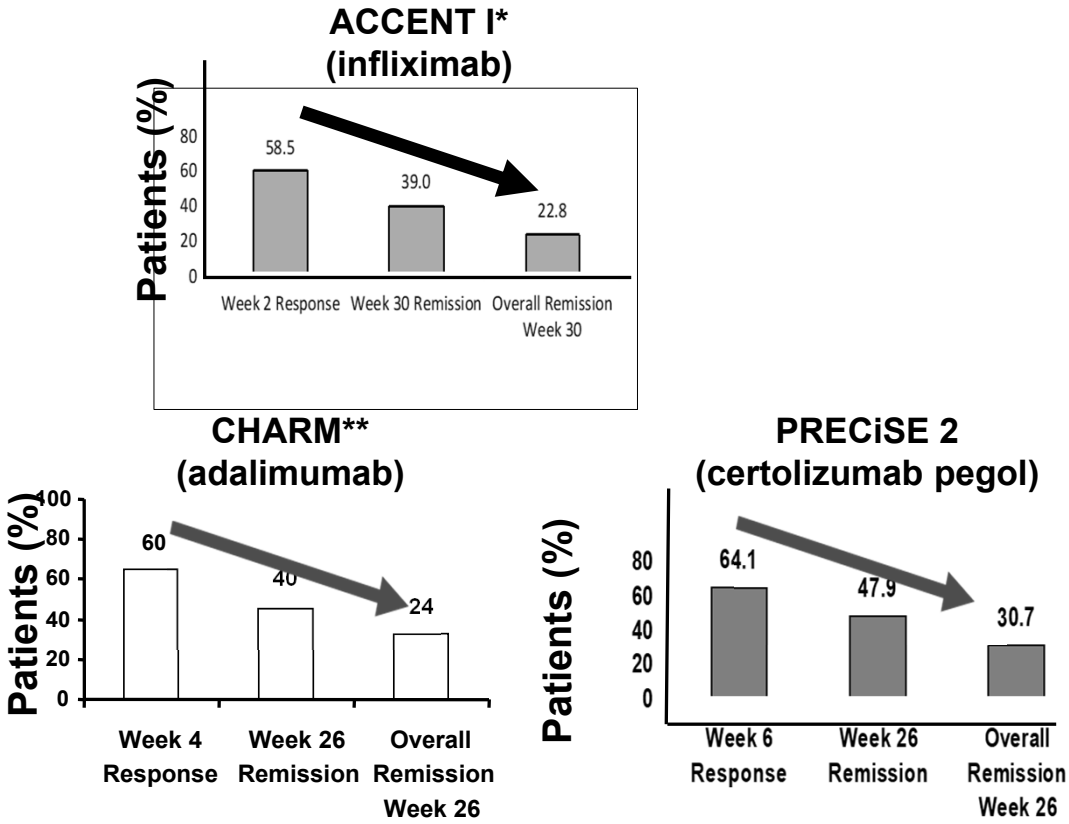
Anti-TNFs and IBD



Anti-TNF agents

- CD: infliximab, adalimumab, certolizumab pegol
- UC: infliximab, adalimumab, golimumab
- Indications
  - Moderate to severe disease
  - Steroid dependent/refractory disease
  - Refractory to immunomodulators
  - Sever, IV steroid refractory UC
  - Fistulizing CD
  - Selected patients with early CD
- Onset of effect: 2-6 weeks

CD: Comparing ACCENT I, CHARM, and PRECiSE 2 Remission Results

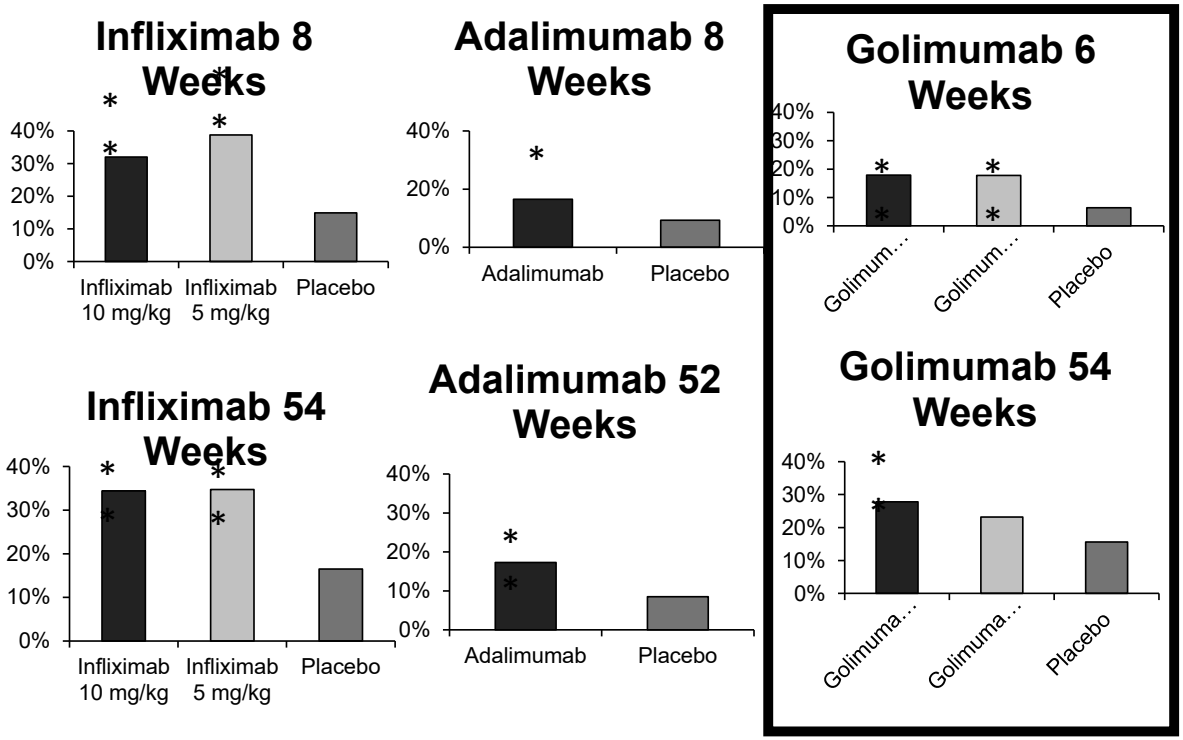


***5 mg/kg dose.**

****Maintenance trial with 80/40 mg induction dosing. Randomized responders = CR-70 at week 4. Week 26 remission among randomized responders on 40 mg every other week dosing.**

Clinical Remission in UC: ACT (Infliximab), ULTRA-2 (Adalimumab) and PURSUIT (Golimumab)

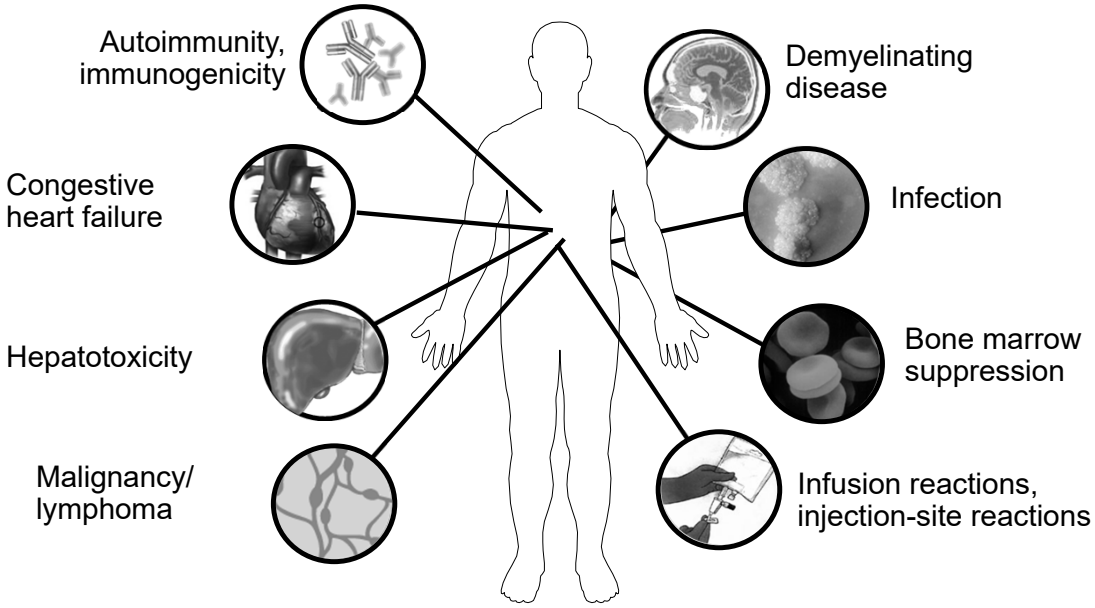
Patients failing 5-ASA/Steroids/IS



*P<0.05 versus placebo; **P<0.01 versus placebo

Sandborn WJ, et al. *Gastroenterology*. 2014;146(1):96-109; Sandborn WJ, et al. *Gastroenterology*. 2014;146(1):85-95; Sandborn WJ, et al. *Gastroenterology*. 2012;142(2):257-265; Rutgeerts P, et al. *N Engl J Med*. 2005;353(23):2462-2476; Panaccione R, et al. *Can J Gastroenterol*. 2008;22(3):261-272.

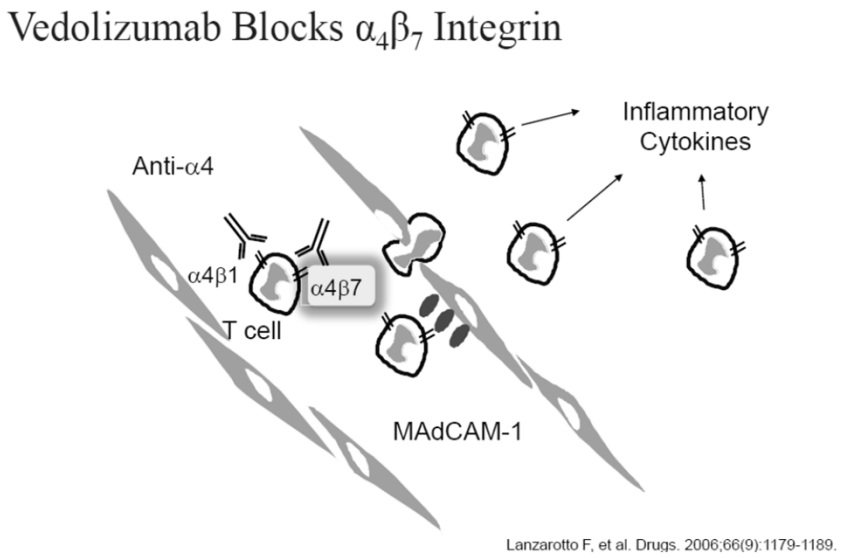
Side effects with anti-TNF therapy



[1]Remicade [package insert]. Horsham, PA: Janssen Biotech, Inc; 2013; [2]Humira [package insert]. North Chicago, IL: AbbVie, Inc; 2013;
[3]Simponi [package insert]. Horsham, PA: Janssen Biotech, Inc; 2013;[4]Bongartz T, et al. *JAMA.* 2006;295:2275-2285.

- These drugs work by binding to integrin subunits and affecting leukocyte trafficking.
- By inhibiting leukocyte trafficking it blocks inflammatory cells from entering the intestine and decreasing inflammation.

Anti-Adhesion Therapy Mechanism of Action



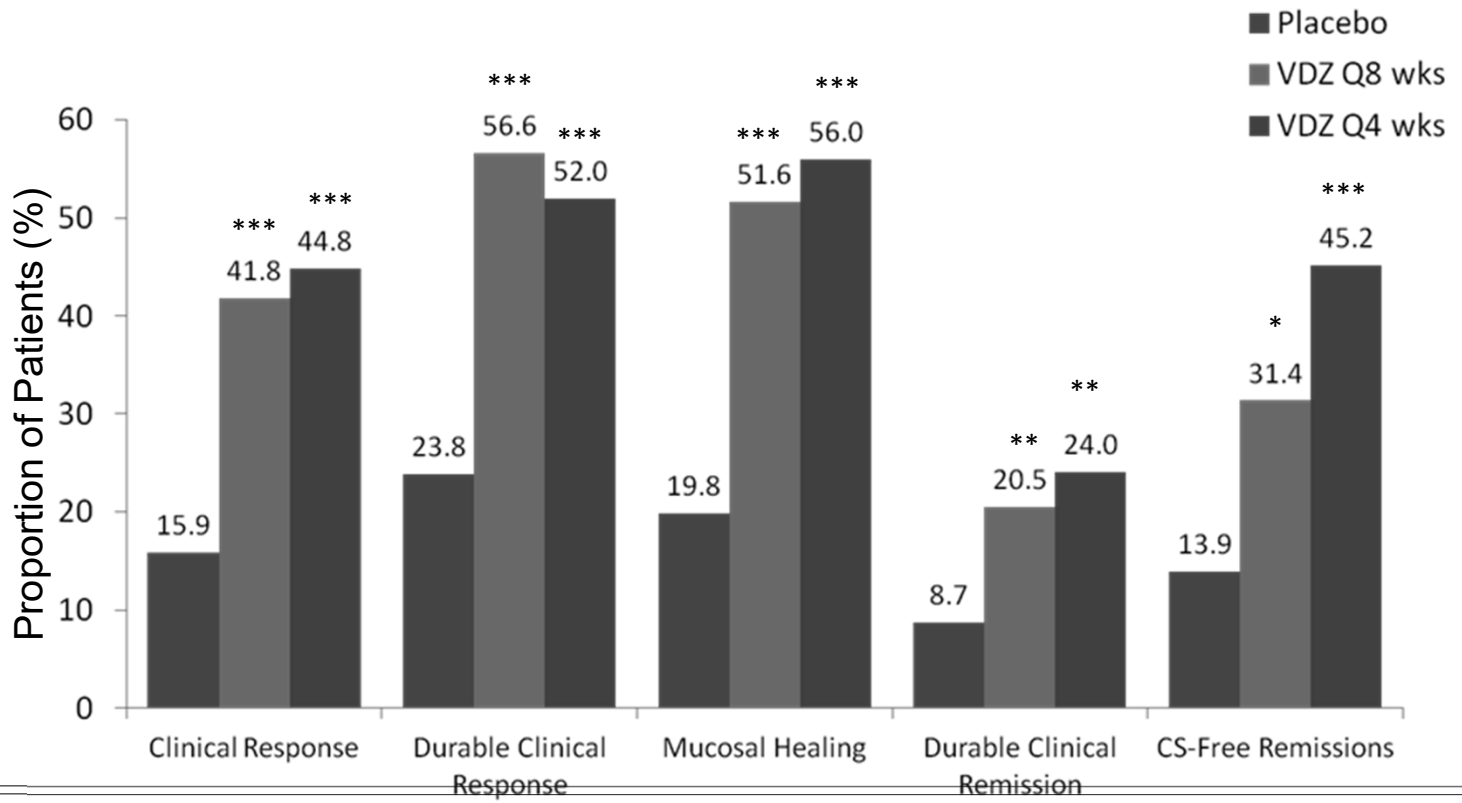
Vedolizumab

- Indications
  - Active UC or CD despite corticosteroids, immune modulators, or anti-TNF
  - Effective in steroids tapering
- Onset
  - As early as 2 weeks
  - 6 to 8 weeks more typical
  - At least 10 weeks needed in CD with prior anti TNF
- Consider using in combination with immune modulators

Sanbron et al, N ENG J Med 2013;369:711-21

Gemini 1: Vedolizumab in UC

Primary and secondary outcomes at week 52



*P<0.05 **P<0.01 ***P<0.0001

Feagan BG. N Engl J Med 2013;369:699-710.

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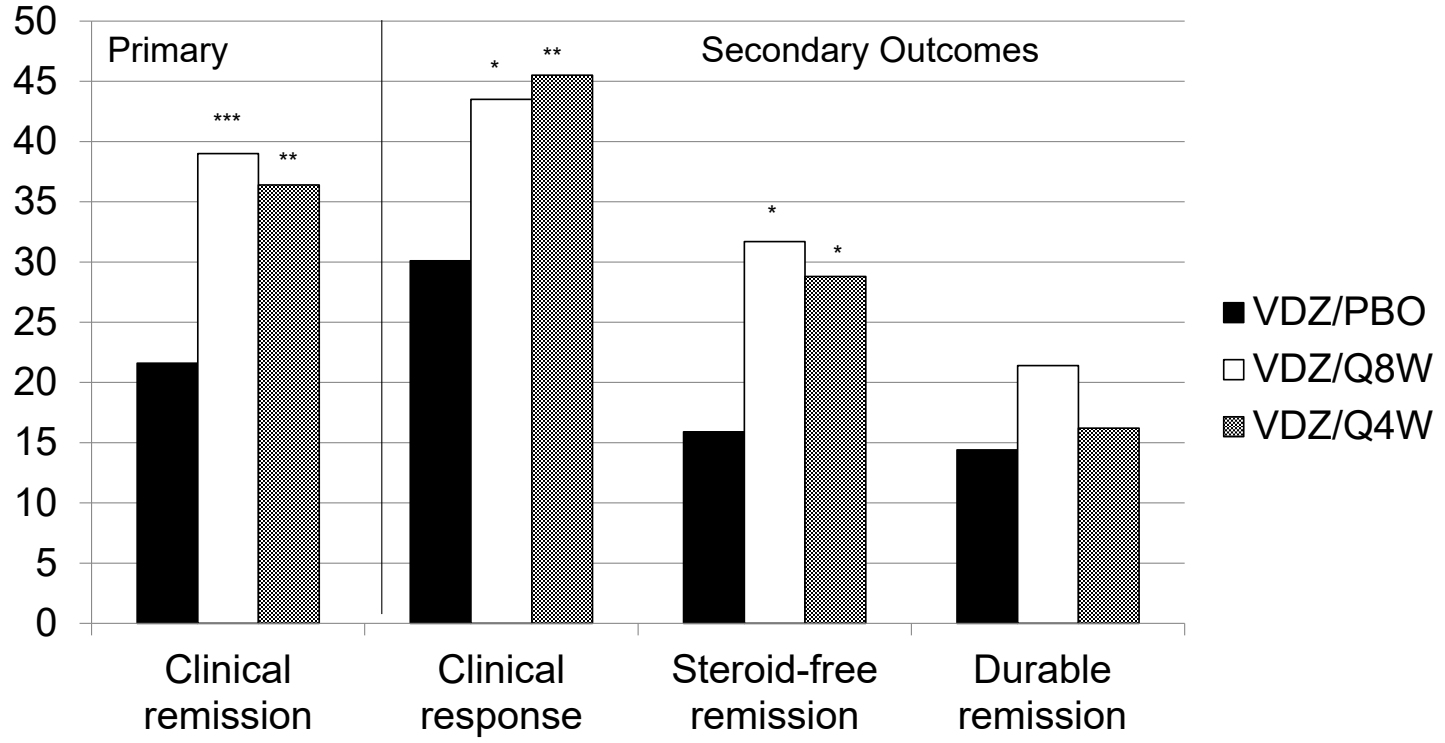
Gemini 2: Vedolizumab in CD

Efficacy at week 52



*P<0.05 **P<0.01 ***P<0.001

Sandborn WJ. N Engl J Med 2013;369:711-721.

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Vedolizumab safety

Infusion-related Reactions	Immunogenicity
• 4 % (vs. 3% placebo) • <1% “severe” • <1% required discontinued therapy • Anaphylaxis: – 1 / 1434 (0.07%)	• 4% anti-vedolizumab antibodies at any time during 52 weeks of study – 16% persistently “+” – 59% neutralizing
PML	**Tuberculosis**
• No cases	• GEMINI 1 - 895 pts: 0 cases • GEMINI 2 - 1115 pts: 1 pt

Entyvio [package insert]. Deerfield, IL: Takeda Pharmaceuticals America, Inc; May 2014.

Where to position vedolizumab in the treatment of IBD

- UC vs. Crohn's disease
  - Vedolizumab is effective in both diseases with steroid-free remission rates of ~30%
    - Onset of action appears to be longer in CD compared to UC (10 weeks vs. 6 weeks)
- Anti-TNF naïve vs. anti-TNF failure
  - Convincing evidence that vedolizumab is more effective when used first-line
- Patients with relative contraindications to anti-TNFs and/or are afraid of anti-TNF side effects
  - Low risk for malignancy, serious infection, OIs, and other systemic toxicity

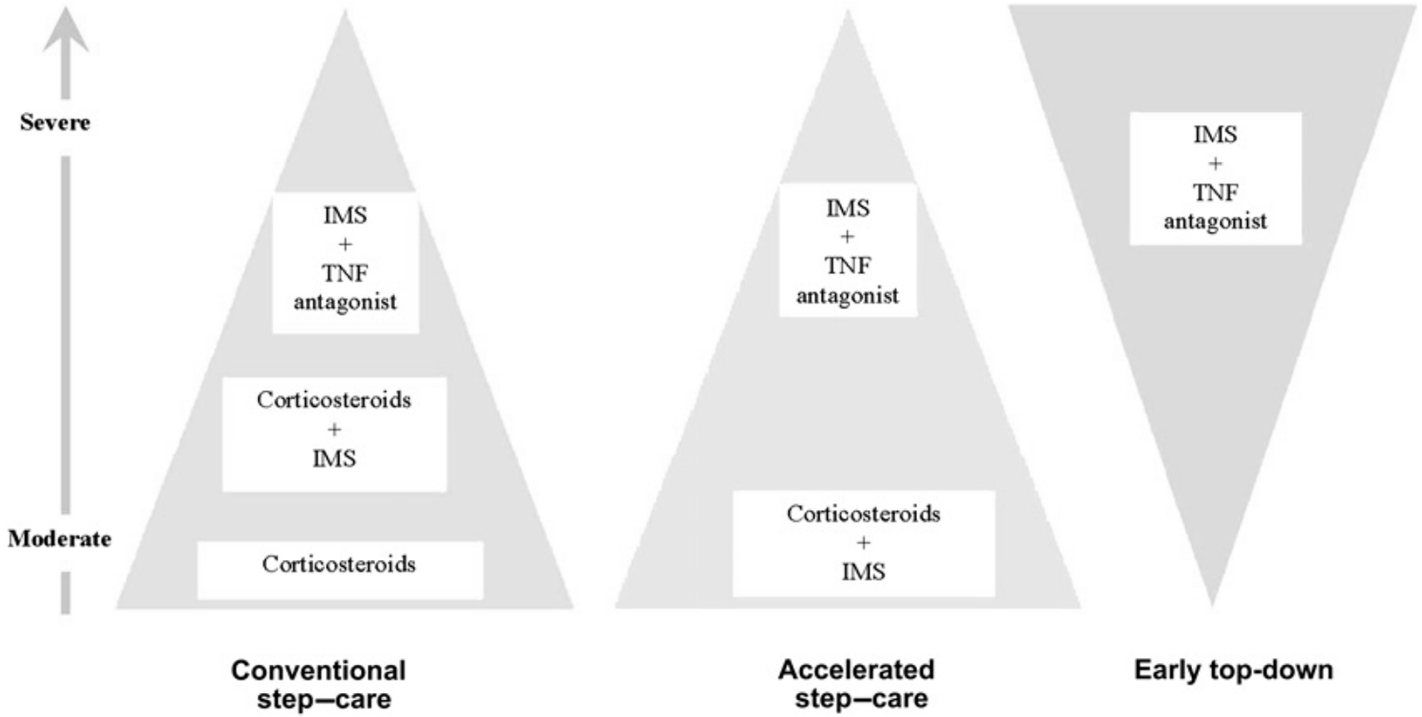
Ustekinumab

- Monoclonal antibody to IL-12 and IL-23
- Indicated for moderately severe Crohn's disease

Tofacitinib

- JAK inhibitor
- Licensed for use in moderately to severely active UC

Conventional and evolving treatment strategies in CD



IMS=immunomodulators

Ordás I et al. Gut 2011

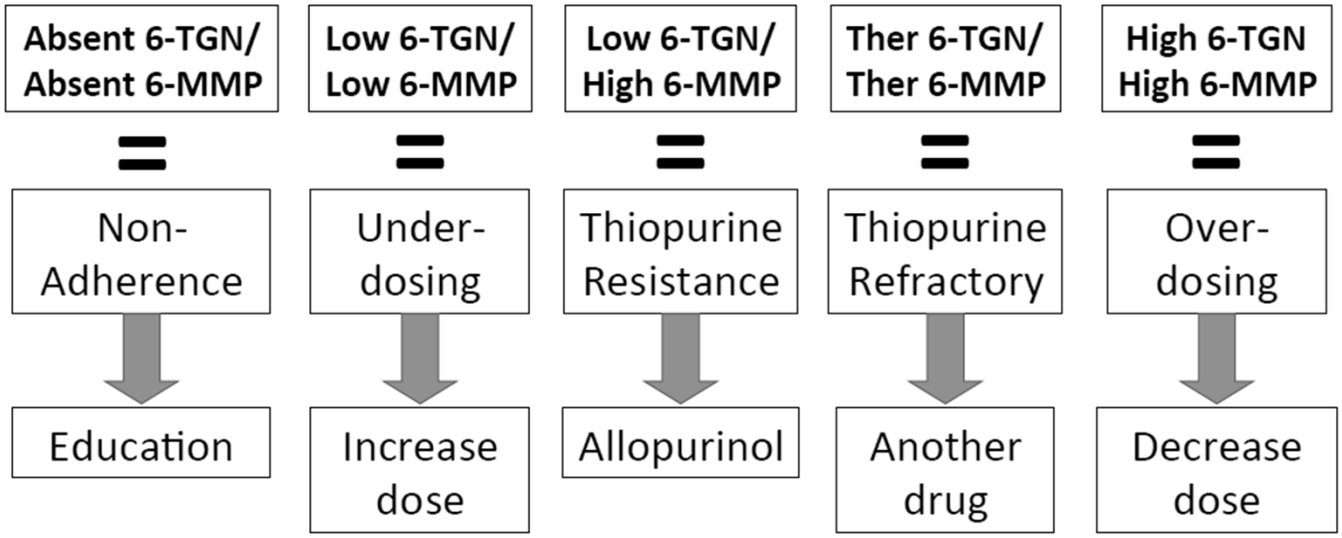
Can we optimize therapy?
What is the role of drug monitoring?

Therapeutic Drug Monitoring

- Measurement of a drug concentration at a pre-specified time point followed by titration of the drug to a target rage.
- Used in other clinical scenarios
  - solid organ transplant
  - use of cyclosporine or tacrolimus in UC
  - use of certain antibiotics
- TDM decreases toxicity and improve outcomes

Thiopurine Metabolites Help Clarify Reasons for Poor Response or Intolerance

- Metabolite measurements are indicated in patients **not responding or experiencing adverse events** to adequate weight-bases doses of thiopurines



Adapted from Gearry RB et al J Gastroenterol Hepatol 2005; 20:1149-57

Loss of Response to TNF inhibitors

- Major limitation of long term TNF therapy
- 13%/year in 16 clinical studies
- In clinical trials up to 40%
- Various mechanism for loss of response including anti-drug antibody (ADA)

Gisbert JP, Panes J. Am J Gastroenterol 2009; 104:760–767

Dose intensification is effective

- ACCENT 1
  - Increase to infliximab 10 mg/kg in patients with luminal CD restored response in 90 % of the patients who lost response to 5 mg/kg
- ACCENT 2

–57% patients with fistulizing CD who lost response on infliximab 5 mg/kg subsequently responded to 10 mg/kg

- Single center experiences

–Pittsburgh: 54 % of patients who received dose intensification regained response and remained on infliximab

Regueiro M , et al. Inflamm Bowel Dis 2007;13:1093-99
Sands BE, et al. Aliment Pharmacol. 2006 ;23:1127-36
Schnitzler F, et al. Gut 2009;58:492-500 r

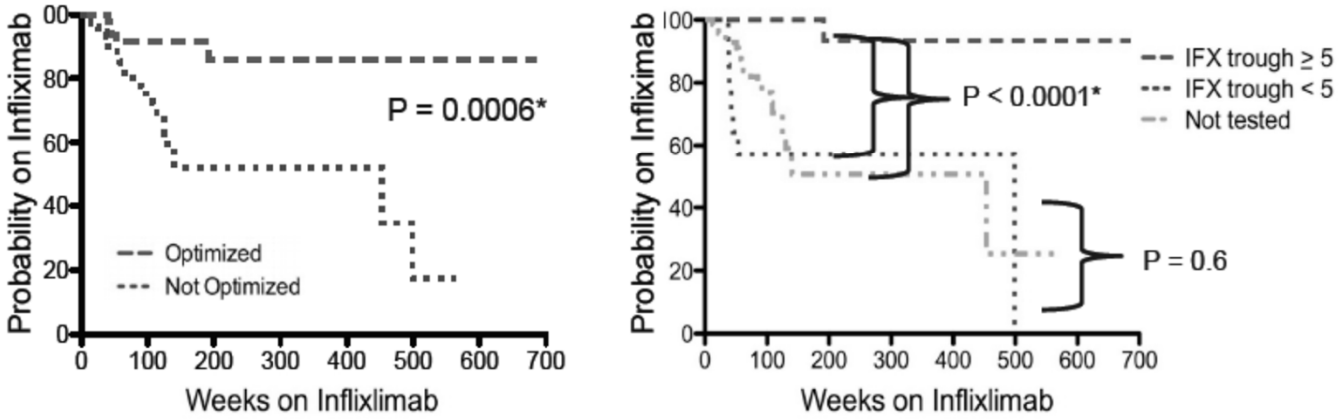
Measuring TNF drug concentrations

Higher levels lead to

- improved mucosal healing
- better endoscopy scores
- longer remission

Prospective Therapeutic Drug Monitoring to Optimize Infliximab Maintenance Therapy in IBD

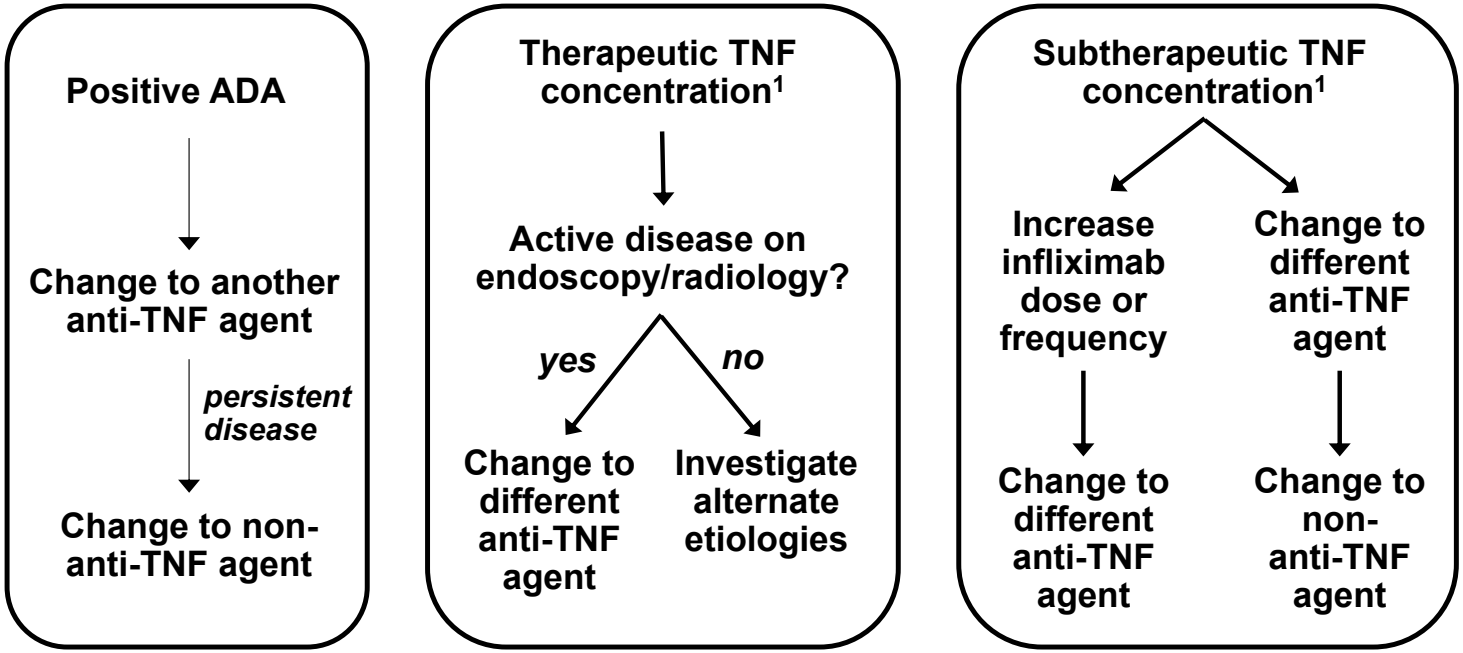
- Retrospective cohort of patients in clinical remission, single physician practice
  - IFX dose optimization to trough concentrations 5–10ug/mL (n=48)
  - No IFX dose optimization (n=78)
- Evaluated probability of remaining on IFX, up to 5 years



Dose optimization increases probability of remaining on IFX therapy up to 5 years

Vaughn BP, et al. Presented at DDW; May 3, 2014 Abstract 209.

Treatment Algorithm for patients with loss of response: TNF and ADA Concentrations



Afif W, et al. *Am J Gastroenterol* 2010;105:1133-9.

Risk of Infection in IBD

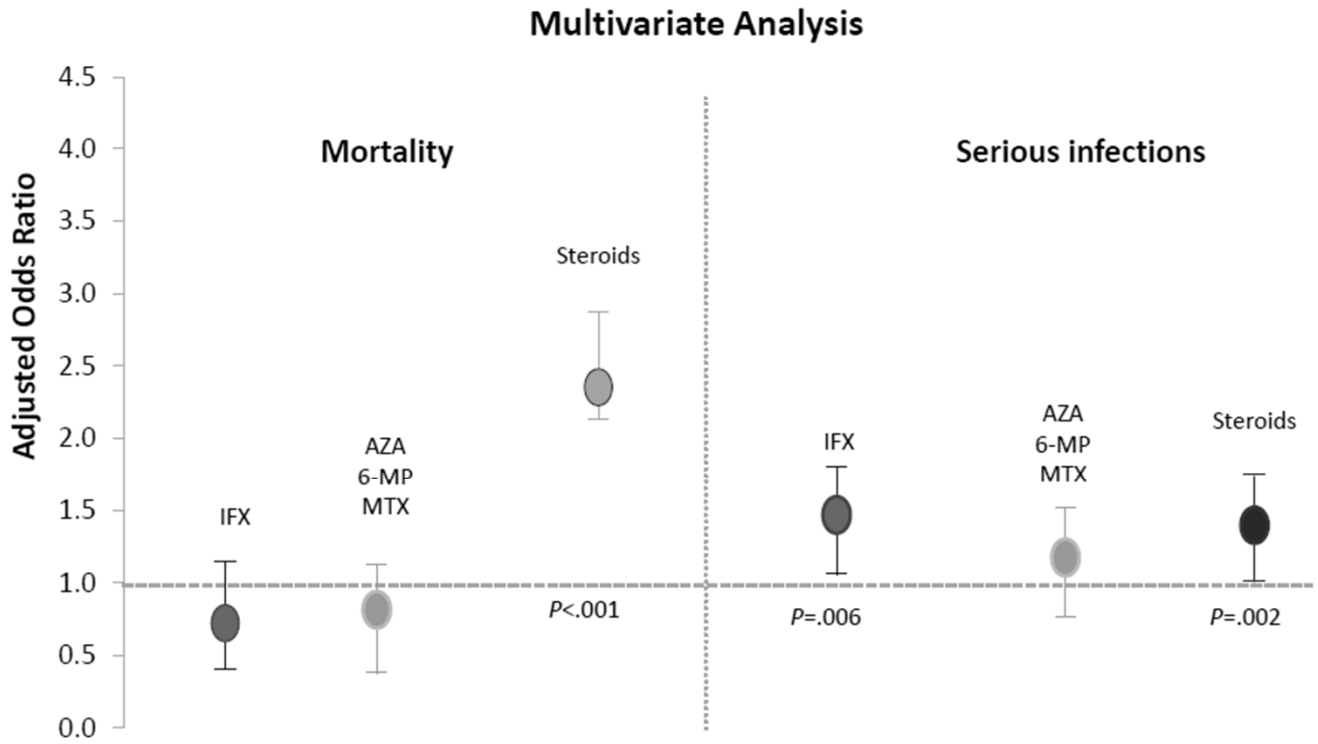
- Infections are the most common significant adverse event among immunosuppressed patient with IBD
- Risk of serious infection increases with the number of immunosuppressive therapies
  - Steroids
- Many infections are preventable with routine preventive immunizations.
- Screening for tuberculosis and hepatitis B recommended prior to initiating therapy
  - Hepatitis C? but TNF agents do not seem to alter course

Zoster

NNH (number needed to harm)	Treatment compared to placebo
Tofa 10mg dailytwice daily	22
Tofa 5mg twice daily	99
Infliximab	231-243
Vedolizumab every 8 weeks	3843
Vedolizumab every 4 weeks	-126

Caldera F Inflamm Bowel Dis 2019

Infections and Mortality in the TREAT Registry: 15,000 Patient-Years of Experience



AZA = azathioprine; IFX = infliximab; MTX = methotrexate.

Lichtenstein GR et al. *Am J Gastroenterol*. 2012;107:1409-1422.

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Vaccination

- IBD itself should not affect vaccine responses
- Goal: prevent infections in a population that is often immunocompromised
  - Influenza, pneumococcal pneumonia, zoster are the most common vaccine preventable illnesses in adults
- Adhere to standard recommended immunization scheduled for adults
- At diagnosis, all adults should have review of immunization history with catch up vaccination given as needed
- Exceptions
  - Live virus vaccines
    - Contraindicated with immunosuppression

Sands et al: IBD 2004;10: 677-92

Summary

- Incidence and prevalence of IBD is increasing
- Treatment options
- Therapeutic drug monitoring is effective in IBD and help recapture clinical remission and can achieve mucosal healing
- IBD patients are under vaccinated and should receive appropriate immunization