NYU Langone Health

Biologic and Small Molecules in the Treatment of IBD

Moderate to Severe IBD: Features

Crohn's Disease

- May require hospitalization
- May have systemic symptoms
- Age < 30 years at presentation
- Disease NOT limited to ileal and right colon
- Deep ulcers
- May have perianal disease
- May have penetrating disease
- Prior surgeries

Ulcerative Colitis

- May require hospitalization
- May have systemic symptoms
- Age < 40 years at presentation
- > 4-5 bowel movements / day
- Extensive disease
- Moderate to severe endoscopic findings
- Possible prior hospitalizations
- Possible prior *C diff* or CMV infection

Sandborn WJ. *Gastroenterology* 2014;147(3):702-705.
Dassopoulos T et al. *Gastroenterology* 2015;149(1):238-245.

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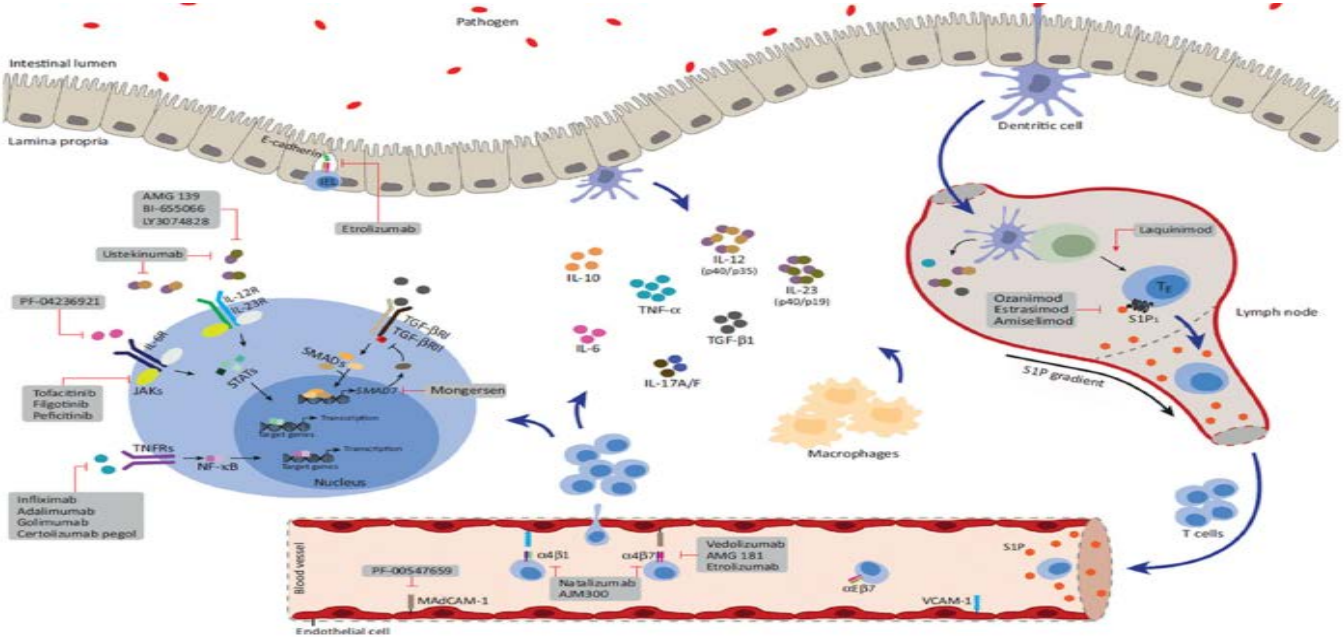
Targets of IBD Therapeutics



Weisshof R, Rubin DT et al. *Adv Ther* 2018;35: 1764-1762.
Coskun M et al. *Trends Pharmacol Sci* 2017;38: 127-142.

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Biologics: Anti-TNF-α Agents

Anti-Tumor Necrosis Factor-α Agents (Anti-TNFs)

- Blocks TNF-α, a cytokine, which modulates immune reactions as an acute phase reactant as well as impacting cell migration, proliferation, and cell death
- Used in Crohn's disease and ulcerative colitis for disease refractory to steroids or when unable to achieve steroid sparing with other agents OR to induce remission in those presenting with more severe disease
- Often used in combination with immunomodulators
- Relatively rapid onset of action (within 2 weeks)
- Prior to initiation must assess for risk of latent or active TB and hepatitis B status

Wang YJ et al. *Cochrane Review DB* 2016.
Lichtenstein GR et al. *Am J Gastroenterol*. 2018;113(4):481-517.
Rubin DT et al. *Am J Gastroenterol*. 2019;114(3):384-413.

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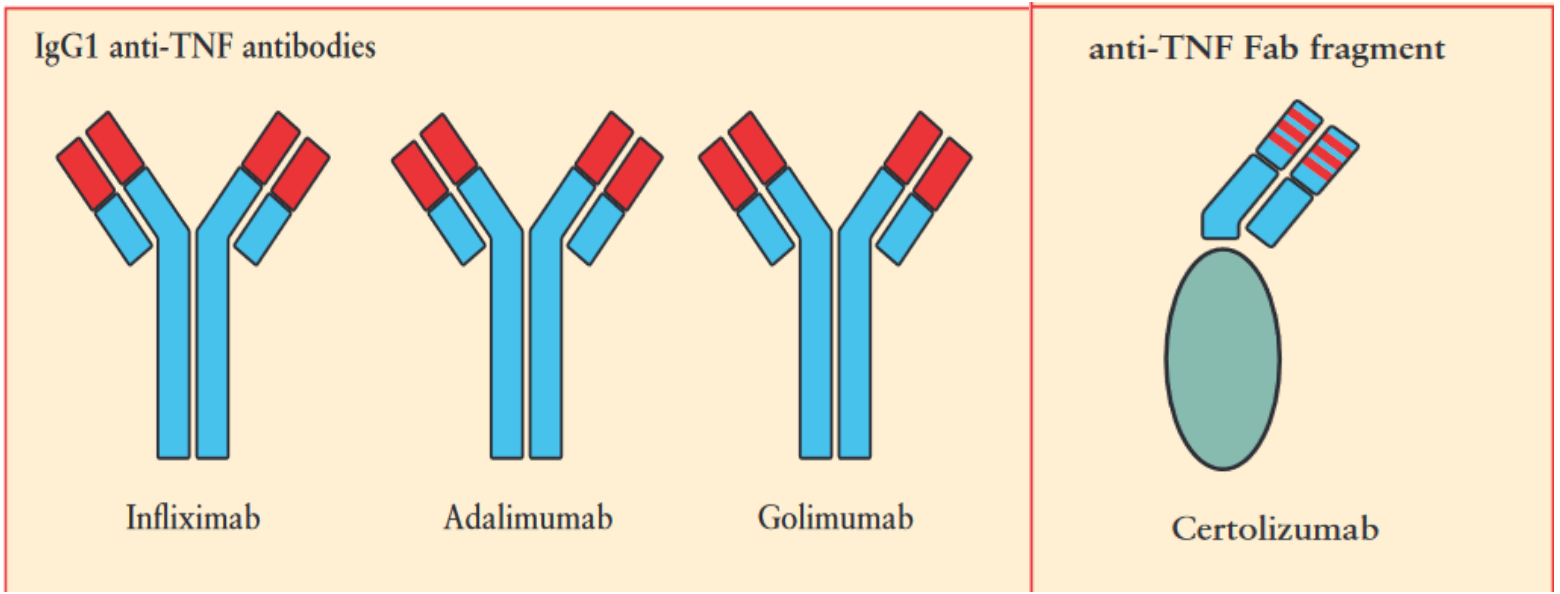
Anti-TNFs



Levin AD et al. *J Crohns Colitis* 2016;10(8):989–999.

Infliximab

- First anti-TNF agent indicated in the treatment of IBD (1998)
- Only FDA-approved agent for fistulizing Crohn's disease
- Chimeric in nature; mouse/human
- Infusion-based treatment
- Dosing:
  - Induction: dose @ 0, 2, and 6 weeks
  - Maintenance: every 8 weeks
  - Infusion takes ~2 hours

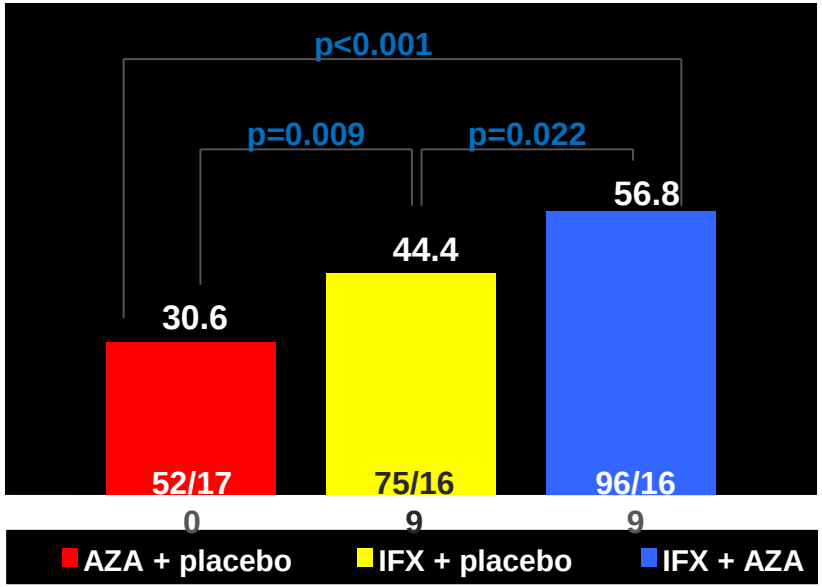
Other Anti-TNFs: Subcutaneous Injectables

Drug	Induction Regimen	Maintenance Regimen
Adalimumab	160mg at 0 weeks 80mg at 2 weeks 40mg at 4 weeks	40mg every 2 weeks
Golimumab (**ulcerative colitis only**)	200mg at 0 weeks 100mg at 2 weeks	100mg every 4 weeks
Certolizumab (**Crohn's disease only**)	400mg at 0 weeks 400mg at 2 weeks 400mg at 4 weeks	400mg every 4 weeks

Combination Anti-TNF and Immunomodulator Treatment

- Combination therapy is favorable as anti-TNFs are immunogenic
- Results in:
  - Reducing anti-drug antibodies
  - Boosting anti-TNF drug levels
- Data for combination is with anti-TNF medications; mainly infliximab with azathioprine
- SONIC trial noted superiority of infliximab + azathioprine compared to either agent alone to achieve steroid-free remission at 26 weeks in CD; UC SUCCESS noted same finding at 16 weeks in UC

Steroid-free Clinical Remission @ Week 26



9 Colombel JF et al. *N Engl J Med* 2010;362:1383-1395.
Panaccione R et al. *Gastro* 2014; 146:392-400.

Anti-TNF: Patient Selection

- Careful patient selection to prevent adverse outcomes is warranted
- Avoid anti-TNFs in patients with:
  - Uncontrolled congestive heart failure Class III & IV
  - Demyelinating conditions
  - Active tuberculosis (TB) infection
  - Prior intolerance to anti-TNFs
- Caution with anti-TNFs in patients with:
  - Prior malignancy
  - Increased risk of infection

Anti-TNF: Safety Profile

- Infusion/injection site reactions: 4% of infusions
- Serum sickness: 2% of patients
- Serious infections: 2% of patients
  - Opportunistic infections: < 0.5%
  - Reactivation of TB
  - Reactivation of hepatitis B virus
- Drug-induced lupus: < 0.5% of patients
- Non-Hodgkin's lymphoma
- Hepatosplenic T-cell lymphoma

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Biologics: Anti-Integrins

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Anti-Integrins: Natalizumab and Vedolizumab

- **Natalizumab**
  - Humanized monoclonal Ab to $\alpha 4$ integrin subunit
  - Non-specific nature of $\alpha 4$ body inhibits lymphocyte trafficking to the CNS
  - FDA approved in Crohn's disease, but use is limited due to risk of progressive multifocal leukoencephalopathy (PML) caused by the JC virus
- **Vedolizumab**
  - Humanized monoclonal Ab targeting $\alpha 4\beta 7$ integrin
  - Targets the interaction with MAdCAM-1; gut-specific
  - No effect on CNS lymphocyte trafficking
  - FDA approved for ulcerative colitis and Crohn's disease in 2014

Sandborn WJ et al. *N Engl J Med* 2005;353(18):1912-1925.
Milch C et al. *J Neuroimmunol* 2013;264(1-2):123-126.

Vedolizumab

- Gemini I & II trials evaluated use in UC and CD respectively
- Gemini III was focused on evaluating response to vedolizumab in prior anti-TNF failures
- Approved in moderate to severe IBD in patients with disease that has:
  - Failed anti-TNF
  - Lost response to anti-TNF
  - Demonstrated failure/intolerance/dependence on steroids
- Dosed at 300mg with induction at weeks 0, 2, and 6 and maintenance infusion every 8 weeks; infusion lasts 30 minutes
- May take 10-12 weeks for clinical response
- Prior to initiation, must assess for risk of latent or active TB and hepatitis B status

Feagin B et al. *N Engl J Med* 2013;369(8):699-710.
Sandborn WJ et al. *N Engl J Med* 2013;369:711-721.
Sands B et al. *Gastroenterology* 2014;147(3):618-627.

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Vedolizumab: Safety Profile

- Safety data from all 6 vedolizumab trials pooled ; up to 5 years of exposure
  - No increased risk of infections (*C diff*, TB, and sepsis < 0.6% patients)
  - No PML
  - < 5% reported infusion reactions
  - 18 malignancies were diagnosed
- Risk / benefit ratio suggests that this drug is favorable for long-term use

Columbel JF et al. *Gut* 2017;66(5):839-851.

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Biologics: Anti-IL 12/23

Ustekinumab

- Novel mechanism of action: binds to p40 subunit of IL-12 and IL-23
- IL-23 contributes to the development of T-helper-17 cells; effector cells in IBD, reducing the cascade of immune cell activation
- IL-12 and IL-23 also play a role in IBD susceptibility
- Humanized IgG1κ monoclonal antibody
- FDA approved for use in Crohn's disease in 2016
- Prior to initiation, assess for risk of latent or active TB and hepatitis B status

Stelara (ustekinumab) for subcutaneous use. Horsham, PA: Janssen Biotech, March 2014 (package insert). Accessed August 2019.
Feagan B et al. *N Engl J Med* 2016;375(20):1946-1960.

Ustekinumab

- UNITI-1 for prior anti-TNF failures / intolerance, UNITI-2 for anti-TNF-naïve patients and IM-UNITI for responders in UNITI-1&2
- Dosing:
  - Infusion is based on weight; **single dose:**

    260mg (< 55kg)

    390mg (55-85kg)

    520mg (> 85kg)
  - Then 90mg injection every 8 weeks

Feagan B et al. *N Engl J Med* 2016;375(20):1946-1960.

Ustekinumab: Safety Profile

- Similar rates of adverse effects in placebo and treatment groups in trials
- Most common: nasopharyngitis and upper respiratory tract infection
- Serious infections: diverticulitis, cellulitis, and pneumonia
- Other: headache, arthralgia, sinusitis, back pain, influenza

Papp KA et al. *Br J Dermatol* 2013;168(4):844-854.
Sandborn et al. *N Engl J Med* 2012;367(16):1519-1528.
Feagan B et al. *N Engl J Med* 2016;375(20):1946-1960.

Small Molecules vs Biologics

Small Molecules	Biologics
Small (single molecule)	Large (mixture)
Simple well-defined structure	Complex heterogeneous structure
Produced by chemical synthesis	Produced in a living cell culture
Non-immunogenic	Immunogenic
Oral administration	Parenteral administration

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Small Molecules

Tofacitinib

- Inhibits the JAK-STAT pathway, which impacts cytokine production and downstream inflammatory cascade
- *In vivo* directly inhibits JAK1 and JAK3
- Great oral bioavailability
- Quick onset; some patients with response within 3 days
- Short half-life
- FDA approved for ulcerative colitis in May 2018

Tofacitinib: Trials

- OCTAVE 1 & 2 are similar trials assessing tofacitinib's ability to induce remission in moderate to severe ulcerative colitis
- OCTAVE sustain trial assessed maintenance in ulcerative colitis
- Anti-TNF-exposed patients responded as well as those who were anti-TNF-naïve
- Taken as a monotherapy
- Dosing at induction is 10mg po bid; response should occur within 8 weeks

  → reduce to 5mg bid

Sandborn WJ et al. *N Engl J Med* 2017;376(18):1723-173.

Tofacitinib: Monitoring

- Check CBC at baseline, 4-8 weeks after starting, and every 3 months
- Interrupt treatment if:
  - Absolute lymphocyte count < 500 cells/mm^3
  - Absolute neutrophil count < 1000 cells/mm^3
  - Hemoglobin < 8g/dL or if hemoglobin declines more the 2g/dL on treatment
- Check lipids at 4-8 weeks after starting to evaluate for dose-dependent changes in lipid profile
- Routine monitoring of liver enzymes

https://www.pfizermedicalinformation.com/en-us/xeljanz , accessed August 19, 2019

Tofacitinib: Safety Profile

- Infection risk
  - UTI or nasopharyngitis are most common
  - Increased risk of herpes zoster; recommend Shingrix to all patients (regardless of age) prior to initiating tofacitinib
- Cardiovascular events seen in those with underlying cardiovascular disease
- Pulmonary embolism: seen in rheumatoid arthritis patients with underlying cardiovascular disease; resulted in new FDA restrictions in July 2019
  - Use in patients who have failed anti-TNF treatment
  - Caution with prior thrombosis
  - Dose reduce to 5mg bid after 8 weeks of therapy
- Gastrointestinal perforation
- Unclear safety profile for pregnancy as of yet

https://www.pfizermedicalinformation.com/en-us/xeljanz , accessed August 19, 2019.

Moderate to Severe IBD: Therapy Considerations

	Adalimumab	Infliximab	Vedolizumab	Tofacitinib	Ustekinumab
Severe Disease	++	+++	++	+++	++
TNF Failure	N/A	N/A	++	Required	+++
Onset of Action	++	+++	++ (naïve)	+++	Pending
Immunogenic	+++	+++	++	N/A	++
Comorbidities	++	++	+++	++	+++
Elderly	++	++	+++	++	+++
Pregnancy	++	++	++	?	++
EIMs	+++	+++	++	+++	+++

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