Biologics: Indications and Optimizing Therapy

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Question 1
Which of the following factors are associated with higher rate of response to anti-TNF therapy?
1. Elevated C-reactive protein
2. Higher trough drug levels
3. Combination with an immune modulator in a naïve patient
4. Continuation of an immune modulator despite ongoing active inflammation
5. 1, 2 and 3
6. All of the above

Question 2
A patient with Crohn's disease is flaring through methotrexate and will be starting treatment with anti-TNF in 1 week. Which of the following should be done?
1. Stop methotrexate
2. Check hepatitis C status
3. Check hepatitis B serologies
4. Administer varicella vaccine if not immune
5. Begin prophylaxis for *Pneumocystis*

Key Points
- Anti-TNF antibodies are the most effective therapies available to treat IBD
- Select patients who will benefit: those with active inflammatory disease, ideally before onset of complicated disease behavior
- Address identifiable safety risks in advance, and educate patient about signs/symptoms of adverse events that are not preventable
- Optimal and more durable response is obtained when combined with an immune modulator

Overview
- Indications and drug selection
- Contraindications and safety
- Optimization
- Controversies
Indications:
Consider the clinical scenario

- Crohn’s disease or ulcerative colitis
- Age of patient
- Severity of flare
- Hospitalized or outpatient?
- Refractory to “conventional therapy”: what came before?
- Fistulizing Crohn’s disease
- Extraintestinal manifestations
- Post-operative prophylaxis in Crohn’s disease?
- Newly diagnosed?

Drug Selection by Indication

<table>
<thead>
<tr>
<th></th>
<th>Infliximab</th>
<th>Adalimumab</th>
<th>Certolizumab Pegol</th>
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<tbody>
<tr>
<td>Luminal CD</td>
<td>✔✔✔</td>
<td>✔✔</td>
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<tr>
<td>Fistulizing CD</td>
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<td>Mild to Moderate UC (Outpatient)</td>
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<tr>
<td>Moderate to Severe UC (Hospitalized)</td>
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<td>Pregnancy</td>
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<tr>
<td>Pouch complications</td>
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<tr>
<td>Extraintestinal manifestations</td>
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Presence of inflammation is the key patient selection factor for treatment with anti-TNF therapy

Patients with Elevated CRP are More Likely to Respond to IFX +/- AZA

Overview

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Contraindications and Safety

- Infection
  - TB
  - HBV
  - HIV
  - Abscess
- Congestive heart failure
- Multiple sclerosis/demyelinating disease
- Lymphoproliferative disorder
- Other cancers

Serious Opportunistic Infections with Anti-TNF Therapy

- Pneumocystis
- Histoplasmosis
- Candidiasis
- CMV
- Atypical mycobacterial infection
- Aspergillosis
- Coccidiomycosis
- Cryptococcosis
- Herpetic
- Salmonellosis
- Legionellosis
- Blastomycosis
- Other

Immunosuppression may impair response to vaccinations

- 96 IBD patients were administered a 23-valent polysaccharide pneumococcal vaccine (PSV-23). Levels of antipneumococcal Antibodies were measured prior to and at least 3 weeks after vaccination.

Special Considerations for Treatment of Fistulas

- Maintain high index of suspicion for abscess
- Evaluate
  - Cross-sectional imaging if intra-abdominal abscess suspected
  - Pelvic MRI and examination under anesthesia if perianal abscess suspected
- Do not treat simple perianal fistulas with anti-TNF
- All abscesses must be drained before starting anti-TNF
- Seton should be placed, if possible before starting anti-TNF for perianal abscess
- Co-treatment with antibiotics appears to be beneficial
- Likelihood of response: perianal > enterocutaneous > rectovaginal > enterovesicular
- Growing role of combined surgical/medical approaches

Vaccines in IBD Patients

- Diagnosis of IBD
  - Check immunization status (MMR, VZV, HepB and Hep A)
  - IS/TNF i/CTS (>20mg)

- Live and live attenuated Vaccines
  - VZV/MMR
  - Others: case by case

- Inactivated vaccines
  - DTP / Hepatitis B / Hepatitis A / influenza / Pneumococcal / HPV (10y) / (if AgHBs-/-/AbAntiC-) (1y) / (if Anti-HAV-) (1y) / (5y) / (F 9-26)

- IS = immunosuppressant; DTP = diphtheria/tetanus toxoids and pertussis vaccine; HPV = human papillomavirus vaccine; MMR = measles, mumps and rubella vaccine; VZV = varicella-zoster virus vaccine.

Ciprofloxacin as an adjunct to infliximab in fistulizing Crohn’s disease

- FIG score at 12 weeks vs. baseline vs. infliximab (p<0.001)
Among patients on concomitant thiopurine and anti-TNF therapies, the absolute risk is under 1:22,000. For patients < 35y:
- Risk of thiopurines monotherapy: 1:7,404
- Risk of combination therapy: 1:3,534

Hepatosplenic T-cell Lymphoma: Should it effect choice of immune modulator?

Defining anti-TNF failure: Secondary Non-response (Loss of Response)
- “Pseudo-failure” for symptoms unrelated to active inflammation
- Pharmacokinetic
  - Inadequate drug levels because of anti-drug antibody
  - Inadequate drug levels because of rapid drug clearance for other reasons
  - Inadequate dose
- Pharmacodynamic
  - Evolution of resistance to anti-TNF mechanism
- Dose-limiting adverse event

Optimal Therapy with Anti-TNFs: Maximizing Efficacy and Avoiding Loss of Response
- Give a loading dose
  - Infliximab 5 mg/kg IV at weeks 0, 2 and 6
  - Adalimumab 160 mg, 80 mg, 40 mg SC EOW
  - Certolizumab pegol 400 mg SC EOW x3
- Give in combination with an immune modulator (mercaptopurine, azathioprine, or methotrexate)
- If not given in combination with immune modulator, give infliximab with hydrocortisone pretreatment
- Avoid episodic dosing
- Consider smoking cessation
- Dose optimize early to avoid unintentional episodic dosing?

Why give concomitant therapy?
- Lower rates of infusion reactions (infliximab)
- Lower rates of anti-drug antibody formation
- Higher drug levels (independent of effect on antibody formation)
- Independent effect of a 2nd active agent
- Lower rate of loss of response
- No signal for increased risk of infection (SONIC)
**Overview**

- Patient selection and indications
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- Drug selection
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**Controversies: Combination Therapy**

- Under what circumstances can concomitant immune modulator be stopped?
- What is the role of concomitant immune modulator in combination therapy after failure of immune modulator?
- Under what circumstances can anti-TNF be stopped?
- What is the role of combination therapy in UC?
- Can lower doses of concomitant immune modulator be used effectively to decrease immunogenicity?
Withdrawal of Concomitant Immune Modulator in Crohn’s Disease While on Infliximab

No need for early ‘rescue’ IFX: primary endpoint

Median IFX levels, Week 8 to Week 104 combined

Controversies: Indications

- When should early aggressive therapy be considered? Can it prevent disease progression?
- For which patients should post-operative prophylaxis be considered?
- Can anti-TNFs be beneficial in stricturing disease?

Controversies: Tailoring Therapy

Background

- We now recognize wide heterogeneity in drug levels
- Heterogeneity in drug levels explains much of the variance in clinical response to drug

Questions

- Is there a therapeutic range for anti-TNF agent drug levels?
- What is the role of anti-drug antibody levels in addressing loss of response?
- Can optimal dosing be predicted before starting therapy through individual factors such as morphometry, biomarkers, and genetics?
- What is the appropriate endpoint in tailored therapy? Should mucosal healing be the goal?

Can biologics decrease surgery in patients with “low-risk” strictures?

Simplified model

Controversies: Tailoring Therapy

Pro

- The inflamed mucosa is the hallmark of active disease
- A healed bowel is the sign of disease control or resolution
- May be achieved with immunomodulators &/or anti-TNFs
- Existing strategies are not effective at longer term control

Con

- Hard to achieve in most patients with existing therapies
- No agreement on definition
  - Partial?
  - Complete?
- Histology?
- Endoscopy?
- Radiographic?
- Cost
- Inconvenience
Elevated Baseline CRP is Associated with Need for Dose Escalation in Anti-TNF-Experienced Patients Treated with Adalimumab

- Weekly dosing of anti-TNF led to greater remission rates when CRP elevated, but not in the group with normal CRP.
- Dose escalation may be most needed and have most benefit in moderate to severe CD patients with prior anti-TNF exposure when CRP is elevated at baseline.

Weekly ADA dosing was associated with higher remission rates than every-other-week (EOW) dosing in anti-TNF-experienced patients with elevated baseline CRP.

Infliximab concentration in ulcerative colitis is associated with albumin level

Infliximab Concentration and Clinical Outcome in Adult Patients with Moderate to Severe UC (ACT 1 & ACT 2)

Patients with Serum IFX Trough Level of >1 µg/mL are More Likely to Achieve Clinical Remission in SONIC

Novel Infliximab and Antibody-to-Infliximab Assays Are Predictive of Disease Activity in Patients with CD

- 1,487 serum samples from 483 participants in 4 CD RCTs/cohorts
- Disease activity measured by CRP
- 1,205 pairs of samples taken over sequential time points (trough infliximab/ATI in first sample, CRP in second sample)
- Predictors of higher CRP: ATI+, infliximab < 3mcg/mL

Conclusions

- Document active inflammation before initiating anti-TNF
- Always consider combination therapy
- Avoid episodic dosing
- Treat active infection before starting anti-TNF
- Prevent preventable infections with vaccination