Treating Inflammatory Bowel Disease with Biologics

Kristen Timperman, PharmD
PGY1 HealthWise Resident
Ohio Northern University
Email: k-timperman@onu.edu

Objectives

1) Review epidemiology, proposed causes, and types of inflammatory bowel disease (IBD)
2) Discuss the pharmacology and adverse effect profile of biologics used in IBD
3) Describe the clinical trial evidence supporting biologics used in IBD
4) Identify the role of biologics in pregnant patients with IBD
5) Review important patient counseling information for patients receiving biologics with IBD
1) Which biologics are currently approved to treat IBD?

I. Natalizumab (Tysabri®)
II. Etanercept (Enbrel®)
III. Infliximab (Remicade®)
IV. Certolizumab pegol (Cimzia®)
V. Adalimumab (Humira®)

a) I, II
b) I, III, IV, V
c) II, III, IV, V
d) All of the above
Do you know?

2. TNF-α inhibitors are safe to use in pregnancy.
   a. True
   b. False
Epidemiology

- More common in northern areas
- More common in industrialized areas
- Incidence: 3.6 to 8.8 per 100,000 persons in the United States
  - Has increased
- Equally affects males and females
- Highest age group affected is 20 to 30 year-olds followed by 60 to 80 year-olds
What is Inflammatory Bowel Disease (IBD)?

- Inflammatory bowel disease (IBD)
  - Types
    1. Crohn’s disease
    2. Ulcerative colitis
  - Exact cause is unknown
  - Inflammatory condition/autoimmune disease
- Different from irritable bowel syndrome (IBS)
**Difference Between Ulcerative Colitis and Crohn’s Disease**

<table>
<thead>
<tr>
<th>Disease Location</th>
<th>Ulcerative Colitis</th>
<th>Crohn’s Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Location</strong></td>
<td>Mainly colon (may affect terminal ileum)</td>
<td>Any portion of the gastrointestinal tract *Rarely patients have gastroduodenal disease</td>
</tr>
<tr>
<td><strong>Lesions</strong></td>
<td>Causes continuous lesions</td>
<td>May cause discontinuous lesions</td>
</tr>
<tr>
<td><strong>Mucosa</strong></td>
<td>Superficial</td>
<td>Transmural (affects deeper portions of the mucosa)</td>
</tr>
</tbody>
</table>
### Difference Between Ulcerative Colitis and Crohn’s Disease

<table>
<thead>
<tr>
<th>Pathologic</th>
<th>Ulcerative Colitis</th>
<th>Crohn’s Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crypt abscesses</td>
<td>Cobblestone appearance</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Complications</th>
<th>Ulcerative Colitis</th>
<th>Crohn’s Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fistulas, perforations, strictures, obstructions are LESS common</td>
<td>Fistulas, perforations, strictures, obstructions are MORE common</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Systemic Signs and Symptoms</th>
<th>Ulcerative Colitis</th>
<th>Crohn’s Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever, malaise, and abdominal pain/tenderness are LESS common</td>
<td>Fever, malaise, and abdominal pain/tenderness are MORE common</td>
<td></td>
</tr>
</tbody>
</table>

- A small fraction of patients show symptoms of both diseases
Difference Between Ulcerative Colitis and Crohn’s Disease
Difference Between Ulcerative Colitis and Crohn’s Disease

From: http://hopkins-gi.org
Etiology
Exact cause is unknown

Thought to be caused by a combination of:

- Abnormal immune response
  - Thought to be a disorder involving T-cells and increased mature B cells
  - Leaky gut
- Infection
- Genetics
- Environment
  - Hygiene hypothesis
• Normal immune system
  ○ Balance of proinflammatory and anti-inflammatory cytokines
    ▪ Proinflammatory: TNF-α, interferon-γ (IFN-γ), interleukin-1 (IL-1), IL-6, IL-12
    ▪ Anti-inflammatory: IL-4, IL-10, IL-11
• This balance of cytokines is disrupted along with the intestinal epithelial barrier
  ○ Leading to destruction of tissue and an activated immune system
Treatment
Goals of Treatment

- Achieve and maintain clinical remission
- Prevent relapses
- Reduce exposure to corticosteroids
- Decrease need for surgeries and hospitalizations
- Improve quality of life
**Pharmacotherapy**

- **5-aminosalicylates: first-line**
  - Mesalamine
  - Sulfasalazine (Azulfidine®)
  - Olsalazine (Dipentum®)
  - Balsalazide (Colazal®, Giazo®)

- **Immunomodulators**
  - Azathioprine (Imuran®)
  - Mercaptopurine (Purinethol®)
  - Methotrexate (Rheumatrex®)
  - Cyclosporine (Sandimmune®)
Pharmacotherapy

• Antibiotics
  o Ciprofloxacin
  o Metronidazole

• Corticosteroids

• Biologics
  o TNF-α inhibitors
  o Leukocyte adhesion and migration inhibitor
Role of Biologics in Treatment of IBD

- Reserved for patients with moderate to severe disease
- Role in fistulizing disease
- TNF-α inhibitors
  - Infliximab (Remicade®)
  - Adalimumab (Humira®)
  - Certolizumab pegol (Cimzia®)
- Alpha-4 integrin inhibitor
  - Natalizumab (Tysabri®)
Biologics: TNF-α Inhibitors
Infliximab
**Infliximab (Remicade®)**

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>MOA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drug Class</strong></td>
<td>TNF-α inhibitor</td>
</tr>
</tbody>
</table>
| **MOA** | Chimeric IgG1 monoclonal antibody  
- Binds intestinal and soluble TNF-α and neutralizes its effect  
- Induces T-cell apoptosis in intestinal cells and peripheral blood monocytes |
<table>
<thead>
<tr>
<th>FDA Indications</th>
<th>Moderate to severe Crohn’s disease, moderate to severe ulcerative colitis, psoriatic arthritis, rheumatoid arthritis in combination with methotrexate, ankylosing spondylitis, plaque psoriasis</th>
</tr>
</thead>
</table>

Infliximab (Remicade®)
# Infliximab (Remicade®)

| **Dose** | Initial dose: 5 mg/kg at 0, 2, and 6 weeks  
Maintenance dose: 5 mg/kg every 8 weeks  
*May increase dose to 10 mg/kg in patients with initial response who lose response (Crohn’s disease labeling) |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Duration of Action</strong></td>
<td>Up to 2 months</td>
</tr>
</tbody>
</table>
## Infliximab (Remicade®)

<table>
<thead>
<tr>
<th>Route</th>
<th>Intravenous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient Assistance Programs</td>
<td>Available at: <a href="http://www.janssenaccessone.com/pages/remicade/patientassist/intro.jsp">http://www.janssenaccessone.com/pages/remicade/patientassist/intro.jsp</a></td>
</tr>
<tr>
<td>Other</td>
<td>Pretreat with corticosteroid (oral prednisone day before infusion or IV hydrocortisone 200 mg on day of infusion), acetaminophen, or diphenhydramine 25 mg po to minimize infusion reaction</td>
</tr>
</tbody>
</table>
# Studies Supporting Efficacy in Crohn’s Disease

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Moderate to severe Crohn’s disease despite other treatment or failed immunomodulator therapy</td>
<td>Patients who maintained their response after 8 weeks of being treated (73 of the 108 patients initially randomized)</td>
</tr>
<tr>
<td>Objective</td>
<td>Determine response rate after 4 wks of single-blind infusion</td>
<td>Determine if sustained efficacy and safety with repeat infusions every 8 weeks for 4 additional infusions</td>
</tr>
<tr>
<td>Drug</td>
<td>Placebo or infliximab 5 mg/kg, 10 mg/kg, 20 mg/kg</td>
<td>Placebo or infliximab 10 mg/kg</td>
</tr>
</tbody>
</table>
### Studies Supporting Efficacy in Crohn’s Disease

|----------------------|--------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|
| Results              | • 65% of patients with infliximab had a ≥ 70 point decrease in the CDAI compared to 17% in control group  
                          • Highest response rate was with 5 mg/kg (81%) over 10 mg/kg (50%) and 20 mg/kg (64%)       | • TREND toward significant response was observed at 44 weeks  
                          • Improved QOL and decreased CRP in infliximab group  
                          • Significant rates of remission were observed at week 44 between infliximab and control (52.9% vs. 20%, p=0.013) |
<p>| Conclusion           | Effective short-term treatment                                                       | Repeated dose maintenance therapy may improve remission rates                         |</p>
<table>
<thead>
<tr>
<th><strong>Inclusion Criteria</strong></th>
<th>573 patients with a CDAI score of &gt; 220</th>
</tr>
</thead>
</table>
| **Design** | • At week 0, all patients received infliximab 5 mg/kg  
  • Response recorded at week 2 and patients divided into 1 of 3 groups (patients followed until week 46)  
    • Group I: placebo at weeks 2, 6, and then every 8 weeks  
    • Group II: infliximab 5 mg/kg at weeks 2, 6, then every 8 weeks  
    • Group III: infliximab 5 mg/kg at weeks 2, 6, then 10 mg/kg every 8 weeks thereafter  
  • At week 14, patients in any group if declining and had a response to infliximab could have step-up therapy |
# Studies Supporting Efficacy in Crohn’s Disease

<table>
<thead>
<tr>
<th>ACCENT I</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Results</strong></td>
</tr>
</tbody>
</table>
| • At week 30, 21% (23/110) of group I, 39% (44/113) of group II (p=0.003), and 45% (50/112) of group III were in remission (p=0.0002)  
• Groups II and III were more likely to sustain clinical remission (odds ratio 2.7, 95% CI 1.6-4.6)  
• Median time to loss of response was 19 weeks for Group I as compared to 38 weeks for Group II (p=0.002) and 54 weeks for Group III (p=0.002)  
• Safety: incidence of serious infections was consistent amongst the groups |
| **Conclusion** |
| Patients who respond to initial dose are most likely to have a longer response time and sustain response if take infliximab every 8 weeks. |
Studies Supporting Efficacy in Crohn’s Disease

- Subanalyses of ACCENT I
  - Demonstrated superiority of scheduled treatment over episodic treatment in maintaining remission. Scheduled group had significantly less hospitalizations.
  - Improved mucosal healing in scheduled group over episodic group.
### Studies Supporting Efficacy in Crohn’s Disease

<table>
<thead>
<tr>
<th>Inclusion Criteria/Design</th>
<th>Prospective multicenter cohort evaluating stopping infliximab in patients who had received at least one year of treatment with infliximab and an antimetabolite</th>
</tr>
</thead>
</table>
| Results/Conclusion        | • Approximately ½ of patients relapsed within 1 to 2 yrs after stopping infliximab  
                          • Factors associated with a lower risk of relapse: fecal calprotectin < 300 μg/g, hemoglobin >14.5 g/dL, WBC ct ≤ 6 x 10⁹/L, hsCRP < 5 mg/L  
                          • Majority of patients retreated with infliximab went back into remission and no patients experienced an infusion reaction = SAFE |
Studies Supporting Efficacy in Crohn’s Disease

- Studies by Present et al, Ardizzone et al, and Sands et al point to infliximab’s utility in fistulizing disease
  - Present et al
    - 68% of the 5 mg/kg group and 56% of the 10 mg/kg group had a > 50% reduction in draining fistulas versus 26% in placebo group (p=0.002 and p=0.02 respectively)
    - 55% of the 5 mg/kg group and 38% of the 10 mg/kg group had closure of all fistulas versus 13% in the placebo group (p=0.001 and p=0.004 respectively)
Studies Supporting Efficacy in Crohn’s Disease

- Studies by Present et al, Ardizzone et al, and Sands et al point to infliximab’s utility in fistulizing disease continued
  - Ardizzone et al
    - Approximately 30% of rectovaginal fistulas healed as compared to 60% of perianal fistulas
    - However, only about 15% of rectovaginal fistulas healed via anal endosonography as compared to about 20% of perianal fissures
    - **Superficial closure of fistulas occurs more easily than deep tract closure**
  - Sands et al
    - 36% of patients in infliximab maintenance group vs. 19% in placebo group had no draining fistulas (p=0.009) at week 54
## Studies Supporting Efficacy in Ulcerative Colitis

<table>
<thead>
<tr>
<th></th>
<th>ACT 1</th>
<th>ACT 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Design</strong></td>
<td>Randomized moderate to severe ulcerative colitis (UC) patients to placebo, infliximab 5 mg/kg, or infliximab 10 mg/kg at weeks 0, 2, 6, and then every 8 wks thereafter through week 46</td>
<td>Randomized ulcerative colitis patients to placebo, infliximab 5 mg/kg, or infliximab 10 mg/kg at weeks 0, 2, 6, 14, and 22</td>
</tr>
<tr>
<td><strong>Results</strong></td>
<td>At week 8, significantly higher 5 mg/kg (64%) and 10 mg/kg (61.5%) achieved clinical response versus placebo (37.2%, p&lt;0.001)</td>
<td>At week 8, significantly higher 5 mg/kg (64.5%) and 10 mg/kg (69.2%) achieved clinical response versus placebo (29.3%, p&lt;0.001)</td>
</tr>
<tr>
<td><strong>Conclusion</strong></td>
<td>Effective in achieving clinical response in UC patients</td>
<td></td>
</tr>
</tbody>
</table>
Summary: Effectiveness of Infliximab

- ~60-70% of patients have an initial response to treatment
- Increase mucosal healing
- Decrease need for surgical interventions and hospitalizations
- Role in fistulizing disease
Adalimumab
Adalimumab (Humira®)

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>TNF-α inhibitor</th>
</tr>
</thead>
<tbody>
<tr>
<td>MOA</td>
<td>Humanized monoclonal antibody</td>
</tr>
<tr>
<td></td>
<td>• Binds TNF-α in the intestinal mucosa and neutralizes its effect</td>
</tr>
<tr>
<td></td>
<td>• Induces T-cell apoptosis in intestinal cells and peripheral blood monocytes</td>
</tr>
<tr>
<td>FDA Indications</td>
<td>Moderate to severe Crohn’s disease, moderate to severe ulcerative colitis, rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, polyarticular juvenile idiopathic arthritis, plaque psoriasis</td>
</tr>
</tbody>
</table>
### Adalimumab (Humira®)

| Dose          | Initial dose: 160 mg (four 40 mg injections on day 1 OR two 40 mg injections per day for 2 consecutive days)  
|               | Second dose: 80 mg 2 weeks later  
|               | Maintenance dose: 40 mg every other week (may increase to 40 mg weekly for Crohn’s disease) |
| Route        | Subcutaneous |
### Adalimumab (Humira®)

<table>
<thead>
<tr>
<th>Dosage Forms</th>
<th>Prefilled syringe or auto-injector pen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient Assistance</td>
<td>HUMIRA protection plan and AbbVie Patient Assistance Foundation</td>
</tr>
<tr>
<td>Programs</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>40 mg/ 0.8 mL</td>
</tr>
</tbody>
</table>

![Diagram of Adalimumab device](http://www.rxabbvie.com/pdf/humira.pdf)
Studies Supporting Efficacy in Crohn’s Disease

- Clinical assessment of adalimumab safety and efficacy studied as induction therapy in Crohn’s disease I (CLASSIC-I) and CLASSIC-II studies: phase III randomized, double-blind, multicenter, placebo-controlled trials
  - CLASSIC-I: induction trial lasting 4 weeks
  - CLASSIC-II: maintenance trial lasting 52 weeks
- Conclusion: demonstrated safety and efficacy of adalimumab therapy in moderate to severe Crohn’s disease
Studies Supporting Efficacy in Crohn’s Disease

- Crohn’s trial of the fully human antibody adalimumab for remission maintenance (CHARM)
  - Phase III trial: 56 week, double-blind, multicenter, placebo-controlled assessing safety and efficacy of adalimumab in moderate to severe Crohn’s disease
  - Open-label induction phase followed by randomization to placebo, adalimumab 40 mg weekly, or adalimumab 40 mg every 2 weeks
  - Conclusion: adalimumab was safe and effective in maintaining remission in moderate to severe Crohn’s disease in weekly and biweekly dosing
Studies Supporting Efficacy in Crohn’s Disease

- Additional long-term dosing with HUMIRA® to evaluate sustained remission and efficacy in CD (ADHERE)
  - Long-term, open-label extension of the CHARM trial
  - Conclusion:
    - 2 years of treatment with adalimumab resulted in decreased hospitalizations, fistula healing, clinical remission, and increased quality of life
    - A sub-analysis suggests patients with disease onset of < 2 yrs and elevated CRP levels have increased benefit
Studies Supporting Efficacy In Ulcerative Colitis

- Ulcerative colitis long-term remission and maintenance with adalimumab treatment of moderate to severe ulcerative colitis 1 (ULTRA 1) and ULTRA 2
  - Randomized, double-blind, multicenter, placebo-controlled trials in patients with moderate to severe ulcerative colitis
  - ULTRA 1 was an 8-week study evaluating induction of clinical remission in those who had not been previously treated with a TNF-α inhibitor and showed adalimumab to be superior to placebo
  - ULTRA 2 was 52-weeks to gather long-term data and demonstrated improved safety and efficacy of adalimumab in the induction and maintenance of remission along with improved mucosal healing over placebo
Certolizumab Pegol
Certolizumab pegol (Cimzia®)

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>TNF-α inhibitor</th>
</tr>
</thead>
</table>
| MOA | Humanized TNF-α Fab monoclonal antibody conjugated to polyethylene glycol  
  • Binds intestinal and soluble TNF-α and neutralizes its effect  
  • Does NOT induce T-cell apoptosis in intestinal cells and peripheral blood monocytes  
  • Does NOT cause complement activation or antibody-dependent cell-mediated toxicity |
# Certolizumab pegol (Cimzia®)

<table>
<thead>
<tr>
<th>FDA Indications</th>
<th>Moderate to severe Crohn’s disease, rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis</th>
</tr>
</thead>
</table>
| **Dose**              | **Initial dose**: 400 mg at weeks 0 and 3  
                        | **Maintenance dose**: 400 mg every 4 wks                                                          |
## Certolizumab pegol (Cimzia®)

<table>
<thead>
<tr>
<th>Route</th>
<th>Subcutaneous</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dosage Forms</strong></td>
<td>Prefilled syringe</td>
</tr>
<tr>
<td><strong>Patient Assistance Programs</strong></td>
<td>CIMplicity patient support program</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td>200 mg/ 1 mL</td>
</tr>
</tbody>
</table>
Studies Supporting Efficacy in Crohn’s Disease

- Winter et al
  - Phase II randomized, placebo-controlled trial
  - Evaluated safety and efficacy of a single dose of IV certolizumab over a 12 week period as compared to placebo in moderate to severe Crohn’s patients
  - Randomized into 1.25 mg/kg, 5 mg/kg, 10 mg/kg, or 20 mg/kg of certolizumab or placebo
  - Conclusion:
    - The amount of patients achieving a clinical response was not significantly different
    - The amount of patients achieving clinical remission was superior at week 2 in the 10 mg group (47.1%) as compared to the placebo group (16%, p=0.041)
Studies Supporting Efficacy in Crohn’s Disease

- Schreiber et al
  - Phase II placebo-controlled study
  - Moderate to severe Crohn’s patients were randomized to either subcutaneous certolizumab 100 mg, 200 mg, or 400 mg or placebo at weeks 0, 4, and 8
  - Conclusion: at all time points except 12 weeks, certolizumab was superior in clinical response to placebo
    - 400 mg dose had the highest response rates which was highest at week 10 (52.8% versus 30.1%, p= 0.006)
    - Patients with CRP levels > 10 mg/L show greater response
Studies Supporting Efficacy

- PRECiSE trials showed previous use of infliximab did not affect response of certolizumab.
- PRECiSE 2 trial showed a positive impact of certolizumab on the health-related quality of life of Crohn’s disease patients, and treatment started closer to diagnosis leads to improved outcomes.
- PRECiSE and WELCOME trial showed certolizumab’s positive effect on Crohn’s patients being able to perform activities of daily living and to remain productive.
Studies Supporting Efficacy

- WELCOME study
  - 26-week study evaluating patients who had previously lost response with infliximab
    - Induction phase was open-label followed by randomized, doubled-blind maintenance therapy
    - At week 26, 40% of patients receiving treatment every 4 weeks and 37% of patients receiving treatment every 2 weeks were in clinical response with 29% and 30% in remission respectively
    - Demonstrated certolizumab as an effective option for patients failing treatment with infliximab
Studies Supporting Efficacy

• MUSIC trial
  ○ Evaluated changes in the intestinal mucosa of patients with active Crohn’s disease who were on long-term therapy with certolizumab
  ○ After 10 weeks of therapy, 62% of patients had endoscopic response and 42% had remission
  ○ After 54 weeks of therapy, 62% had endoscopic response and 28% had remission
Loss of Effectiveness with TNF-α Inhibitors
Loss of Effectiveness with TNF-alpha inhibitors

• ~40% of patients maintain the response at 1 year or stay in remission
• Anti-drug antibodies (ADA) may play a role
  ○ Typically are IgG antibodies which bind to biologic proteins decreasing efficacy
  ○ May increase clearance of the drug
  ○ Contribute to infusion reactions and decreased responsiveness of the medication
  ○ Incidence: 10-20% of patients on anti-TNF therapy
Loss of Effectiveness

- If loss of effectiveness to one TNF-α inhibitor, may switch to another medication in the same class, increase dose, or increase dosing frequency
  - Secondarily, may switch to a non-TNF-α inhibitor medication
Biologics: Alpha-4 Integrin Inhibitors
Natalizumab

From: http://www.heplive.com/articles/Natalizumab-Promising-for-Teens-With-Multiple-Sclerosis
### Natalizumab (Tysabri®)

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Selective adhesion-molecule inhibitor</th>
</tr>
</thead>
</table>
| MOA              | Recombinant humanized IgG4 monoclonal antibody  
• Leukocyte adhesion and migration inhibitor by inhibiting the α4 subunit of integrin |
| FDA Indication   | Moderate to severe Crohn’s disease, multiple sclerosis |
Mechanism of Action

From: http://www.ajnr.org/content/31/9/1588/F2.expansion.html
# Natalizumab (Tysabri®)

<table>
<thead>
<tr>
<th>Dose</th>
<th>300 mg IV every 4 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Route</td>
<td>Intravenous</td>
</tr>
</tbody>
</table>
| Other      | • Only available via the manufacturer’s TOUCH prescribing program  
|           | • Observe patients during and for 1 hour after the infusion |
Studies Supporting Efficacy

- Phase II trials
  - Demonstrated efficacy of natalizumab IV at doses of 3 mg/kg, 3 mg/kg every 4 wks x 2 doses, and 6 mg/kg every 4 wks x 2 doses
- Phase III trials
  - Natalizumab 300 mg IV every 4 wks for 6 months showed benefit of maintenance treatment greater than 30% over placebo
  - Patients with an increased CRP level have increased benefit
Studies Supporting Efficacy

- Evaluation of natalizumab in active Crohn’s disease therapy-2 study (ENATC-2)
  - Randomized, double-blind, placebo-controlled trial, multicenter study
  - Conclusion: demonstrated ability to taper corticosteroids off while continuing to achieve clinical response and/or remission
Studies Supporting Efficacy

- Has also demonstrated benefit in ulcerative colitis patients
  - Patients received a single 3 mg/kg infusion
  - Conclusion: decrease in disease severity
Safety of Biologics
Safety: TNF-α Inhibitors
Contraindications

- Infliximab
  - Doses > 5 mg/kg in moderate to severe heart failure
  - Hypersensitivity to infliximab or murine protein
- Adalimumab
  - None
- Certolizumab pegol
  - None
Warnings and Precautions

- Serious infections
- Invasive fungal infections
- Malignancies
- Hepatitis B virus reactivation
- Hepatotoxicity*

*Infliximab only

- Heart failure
- Cytopenias
- Hypersensitivity
- Demyelinating disease
- Lupus-like syndrome
- Live vaccines
Class Adverse Effects

- Many are due to these products suppressing the immune system
- Side effects among the different biologics are similar
- Short-term side effects are low
- Risk of long-term, more serious side effects is more unclear
Class Adverse Effects: Black Box Warnings

- Serious infection
  - Increased risk of serious infections leading to hospitalization or death, including TB, bacterial sepsis, invasive fungal infections, and infections due to other opportunistic pathogens.
  - Discontinue if develop serious infection.
  - Perform test for latent TB; if positive, start treatment before anti-TNF therapy. Monitor patients for active TB during therapy.
Class Adverse Effects: Infection Risk

- Pneumonia
- Sepsis
- Tuberculosis
- Disseminated coccidiomycosis
- Histoplasmosis
- Listeriosis
- Aspergillosis
- Hepatitis B reactivation
Class Adverse Effects: Black Box Warnings

- Malignancy
  - Lymphoma and other malignancies, some fatal, have been reported in children and other adolescents treated with TNF blockers.
  - Postmarketing cases of fatal hepatosplenic T-cell lymphoma (HSTCL) have been reported in patients treated with TNF blockers. Majority were adolescent or young adult males. All had received prior concomitant therapy with 6-mercaptopurine or azathioprine.
Class Adverse Effects: Serious

- Heart failure
- Lupus-like syndrome: shortness of breath, joint pain, rash on arms or face
- Decreased blood cell counts
- Nervous system problems: seizures, multiple sclerosis, optic neuritis
- Hypersensitivity reactions
Class Adverse Effects: Less Serious

- Hypersensitivity reactions: injection site reactions
- Upper respiratory infections
- Bladder infection
- New or worsening psoriasis
Safety: Alpha-4 Integrin Inhibitor
## Contraindications & Warnings and Precautions

<table>
<thead>
<tr>
<th>Contraindications</th>
<th>Warnings and Precautions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current or history of progressive multifocal encephalopathy (PML)</td>
<td>Serious infections including herpes encephalitis and meningitis</td>
</tr>
<tr>
<td>Hypersensitivity to natalizumab</td>
<td>Hypersensitivity reactions</td>
</tr>
<tr>
<td></td>
<td>Hepatotoxicity</td>
</tr>
</tbody>
</table>
Adverse Effects: Black Box Warning

- Increased risk of progressive multifocal leukoencephalopathy (PML), a viral opportunistic infection of the brain which generally leads to serious disability or death
- Risk factors are duration of therapy, anti-JCV antibodies, and prior use of immunosuppressants. Weigh risk versus benefits before starting
- Stop treatment at first sign of PML
- Only available through restricted distribution program, TOUCH
Progressive Multifocal Leukoencephalopathy

- Caused by the JC virus
- Signs and symptoms
  - Progressive weakness on one side of the body
  - Loss of control of limbs
  - Visual changes
  - Confusion
  - Personality changes
- Death or severe disability typically results in weeks to months
  - No adequate treatment
Adverse Effects

- Incidence > 10%
  - Headache
  - Fatigue
  - Arthralgia
  - Diarrhea
  - Abdominal discomfort
  - Nausea
  - Rash
  - UTI
  - Lower RTI
  - Gastroenteritis
  - Vaginitis
  - Depression
  - Pain in the extremity
Biologics in Pregnancy
IBD in Pregnancy

- Diagnosis is often made during the childbearing years
- Goal is to achieve and maintain remission prior to pregnancy
- Prior to conception, make sure receiving folate, calcium, and vitamin D supplements
IBD: Fertility and Trait Inheritance

*Fertility*
- Typically the same as non-IBD patients
- Exceptions:
  - Patients with ileal pouch anal anastomosis (IPAA)
  - Crohn’s disease patients with inflammation affecting colon, fallopian tubes, or ovaries
- Medications do NOT decrease female fertility
Ileal Pouch Anal Anastomosis

Prior To Surgery (Normal)

With Diverting Ileostomy

After Ileostomy Takedown

Controls

Visit 1

Visits 2, 3, 4

IPAA Patients

From: http://www.microbiomejournal.com/content/1/1/9/figure/F1
• Risk of passing trait on to children
  ○ ~7% with Crohn’s and less with ulcerative colitis
  ○ ~37% if both parents have the disease
IBD Effects on Pregnancy

- Typically disease will be of the same intensity it was when conception occurred
  - Crohn’s disease may flare in 2\textsuperscript{nd} and 3\textsuperscript{rd} trimesters
  - Ulcerative colitis may flare in 1\textsuperscript{st} trimester and post-partum period
IBD Effects on Pregnancy

- Typically no adverse effects on fetus
- Possible increased risk of preterm delivery and low birth weight
IBD Effects on Delivery

- Most patients can have a normal vaginal delivery
- Caesarean section is advised for patients with:
  - Peri-anal disease
  - Ileal pouch anal anastomosis
- Increased risk of a venous thromboembolism (VTE)
Biologics in Pregnancy

• TNF-α inhibitors: infliximab (Remicade®), adalimumab (Humira®), certolizumab pegol (Cimzia®)
  ○ No increased risks of stillbirths, spontaneous abortions, or miscarriages
  ○ Does NOT pass into breast milk
  ○ Pregnancy category B
  ○ Thought to be SAFE
  ○ Avoid administration of live vaccines to infants until >6 mo of age
Biologics in Pregnancy

- Alpha-4 integrin inhibitor: natalizumab (Tysabri®)
  - Pregnancy category C
  - Limited information
  - Use when benefit outweighs risk
Recent News for IBD

- **Pregnancy in Inflammatory Bowel Disease and Neonatal Outcomes: A National Prospective Registry (PIANO study)**
  - Started in August 2007
  - Enrolled over 1115 patients across the United States (896 delivered)
  - Objective: to determine whether there is a higher rate of adverse events in a prospective national sample of women from the US with IBD who are being treated with azathioprine/6MP or anti-TNF biologic drugs (infliximab, adalimumab, certolizumab). It compared women on these medications to women on no medications.
  - Data collection: each trimester of pregnancy, at delivery, and every four months in the first year of the child's life.
Recent News for IBD

- **PIANO study continued**
  - Some children will be followed until the age of 4 to look for an infection risk or other adverse effects from taking biologics
  - **Results**
    - IBD meds appear to be safe during pregnancy: not associated with congenital anomalies or altered newborn growth and development
    - Biologic therapy only: slight increased risk of C-sections and spontaneous abortions
    - Combination therapy: slight increased risk of preterm birth and infant infections at 12 months
    - No change in risk of infant infection with breastfeeding
Patient Counseling Information
Infection Control

- Latent tuberculin skin test prior to treatment
- If hepatitis B positive, complete treatment prior to biologic initiation
- Ensure vaccine status is up to date
  - Do not take live vaccines during treatment
  - Yearly influenza vaccine
- Avoid consumption of unpasteurized dairy products
- Consider omitting dose of therapy around surgeries due to infection risk
  - Prosthetic valves
Nutritional Support

- Nutritional deficiencies are common in IBD
- Multivitamin
  - Folic acid and vitamin B12
- Calcium and vitamin D
  - IBD is a risk factor for osteoporosis along with chronic steroid use
- Food diaries
  - Identify association of food triggers with bowel symptoms
  - Triggers are unique for each patient
Probiotics

- Conflicting evidence on efficacy
- Considered to be safe
- VSL #3 has shown to be effective in decreasing flares in patients with pouchitis
Colonoscopies

- Patients are at an increased risk of colon cancer
  - Additional risk factors
    - Early age of onset
    - Disease duration
    - Extent of involvement
    - Family history of colorectal cancer
- Frequency of colonoscopy depends on the extent and severity of disease
Stress Reduction

- Acupuncture and acupressure
- Meditation
- Deep breathing exercises
- Exercise
Medications to Avoid

- NSAIDs
  - Increased bleeding risk
  - Increased risk of disease flares
Injection Instructions for Subcutaneous Biologics

- **Injection sites:** thigh or stomach
Injection Instructions for Subcutaneous Biologics

- **Administration:**
  - Check the expiration date before injecting
  - Do **NOT** use if the medication is cloudy or has large particles in it
  - Wipe the injection site with an alcohol swab
  - Inject at least 2 inches away from the belly button
  - Do **NOT** inject in any area that is bruised, red, or swollen
  - Rotate injection sites

- **Helpful tip:** ice can be used to help numb the area before the injection
Storage Instructions for Subcutaneous Biologics

- Keep in the refrigerator
- Do **NOT** freeze
- Store in original package
1) Which biologics are currently approved to treat IBD?

I. Natalizumab (Tysabri®)
II. Etanercept (Enbrel®)
III. Infliximab (Remicade®)
IV. Certolizumab pegol (Cimzia®)
V. Adalimumab (Humira®)

a) I, II
b) I, III, IV, V
c) II, III, IV, V
d) All of the above
1) **Which biologics are currently approved to treat IBD?**

I. Natalizumab (Tysabri®)
II. Etanercept (Enbrel®)
III. Infliximab (Remicade®)
IV. Certolizumab pegol (Cimzia®)
V. Adalimumab (Humira®)

a) I, II  
b) I, III, IV, V  
c) II, III, IV, V  
d) All of the above
2. TNF-α inhibitors are safe to use in pregnancy.

a. True

b. False
2. TNF-α inhibitors are safe to use in pregnancy.
   a. True
   b. False
References

References

References

References

References