PHARMACOLOGIC MANAGEMENT FOR INFLAMMATORY BOWEL DISEASE: ULCERATIVE COLITIS & CROHN’S DISEASE

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AtlantiCare Regional Medical Center
OBJECTIVES

• Differentiate between the various oral mesalamine preparations for Ulcerative Colitis & Crohn's Disease

• Describe the pharmacologic actions of anti-TNF monoclonal antibody therapies for Inflammatory Bowel Disease
We’ve come a long way…

IBD is recognized

Crohn’s & UC described

Prednisone
Sulfasalazine

Azathioprine
Methotrexate

Mesalamine

Remicade
Humira
Cimzia
Tysabri
Goals of Therapy in the Inflammatory Bowel Diseases

Symptom Improvement

Improve the Future
• Reduce Hospitalization
• Reduce need for surgery
• Reduce social & occupational burden

Mucosal Healing

Targeted Therapy Against Inflammation in IBD

Improve Safety and Tolerability of Medications
### Differences Between Crohn's Disease and UC

<table>
<thead>
<tr>
<th></th>
<th>Crohn's Disease</th>
<th>Ulcerative Colitis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Location</strong></td>
<td>Affect any part of the GIT, from <em>mouth</em> to <em>anus</em></td>
<td>Restricted to colon &amp; rectum</td>
</tr>
<tr>
<td><strong>Distribution</strong></td>
<td>Patchy areas of inflammation</td>
<td>Continuous area of inflammation</td>
</tr>
<tr>
<td></td>
<td><em>Skip lesions</em></td>
<td></td>
</tr>
<tr>
<td><strong>Depth of inflammation</strong></td>
<td>Deep into tissues</td>
<td>Shallow, mucosal</td>
</tr>
<tr>
<td><strong>Complications</strong></td>
<td>Strictures, Obstruction, Abscess, Fistula</td>
<td>Toxic megacolon, Colon cancer</td>
</tr>
</tbody>
</table>
The Spectrum of IBD

Inflammatory Bowel Diseases (IBD)
>1 million persons in the United States

- Ulcerative Colitis (UC)
  - Proctitis
  - Pancolitis
  - Left-Sided Disease

- Indeterminate colitis
  - Gastro-duodenitis
  - Ileitis
  - Ileocolitis

- Crohn’s disease (CD)
  - Perianal disease
  - Colitis

Ulcerative colitis

Crohn's disease

<table>
<thead>
<tr>
<th>Feature</th>
<th>Crohn's disease</th>
<th>Ulcerative colitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical features</td>
<td>Fairly common</td>
<td>Very common</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>Fairly common</td>
<td>Very common</td>
</tr>
<tr>
<td>Rectal bleeding</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sites of involvement</td>
<td>50% of patients</td>
<td>Never</td>
</tr>
<tr>
<td>Ileum and colon (ileocolonic region)</td>
<td>30% of patients</td>
<td>Never</td>
</tr>
<tr>
<td>Ileum</td>
<td>20% of patients</td>
<td>Exclusively</td>
</tr>
<tr>
<td>Colon</td>
<td>Infrequent</td>
<td>Never</td>
</tr>
<tr>
<td>Upper parts of GIT</td>
<td>Discontinuous lesions, cobblestoning, aphthous and linear ulcerations, strictures</td>
<td>Continuous lesions, pseudopolyps</td>
</tr>
<tr>
<td>Endoscopic findings</td>
<td>Transmural inflammation</td>
<td>Mucosal/submucosal inflammation</td>
</tr>
<tr>
<td>Histologic findings</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
CANCER RISK AND IBD

• No increased risk with proctitis

• Cumulative Ca rate (3 centers) for UC = 7.2% @ 20 years, 16.5% @ 30 years

Conclusion: Similar risk of CD as with UC

Colon Cancer Prevention in UC

• 81% reduction with “regular” 5-ASA use.

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3 Edwards FC, Truelove SC. Gut 1964; 5:15-22
5 Pardi S. Gastroenterology 2003; 124:889-893
# EXTRAVENOUS MANIFESTATIONS

**Table 1** Major extraintestinal immune-related manifestations of IBD

<table>
<thead>
<tr>
<th>Arthritis</th>
<th>Erythema nodosum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pyoderma gangrenosum</td>
<td>Aphthous stomatitis</td>
</tr>
<tr>
<td>Iritis/uveitis</td>
<td></td>
</tr>
</tbody>
</table>

**Table 2** Autoimmune disorders associated to IBD

<table>
<thead>
<tr>
<th>Alopecia areata</th>
<th>Ankylosing spondylitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bronchiolitis obliterans</td>
<td>Cold urticaria</td>
</tr>
<tr>
<td>Hemolytic anemia</td>
<td>Henoch-Schoenlein purpura</td>
</tr>
<tr>
<td>Insulin-dependent diabetes mellitus</td>
<td>Pancreatitis</td>
</tr>
<tr>
<td>Primary biliary cirrhosis</td>
<td>Primary sclerosing cholangitis</td>
</tr>
<tr>
<td>Polyarteritis</td>
<td>Raynaud phenomenon</td>
</tr>
<tr>
<td>Seropositive rheumatoid arthritis</td>
<td>Sjogren syndrome</td>
</tr>
<tr>
<td>Thyroid disease</td>
<td>Vitiligo</td>
</tr>
<tr>
<td>Wegener’s granulomatosis</td>
<td>Takayasu’s arteritis</td>
</tr>
</tbody>
</table>

**Table 3** Extraintestinal complications in IBD and principal pathogenetic mechanisms of arthritis

<table>
<thead>
<tr>
<th>Extraintestinal complications in IBD</th>
<th>Principal pathogenetic mechanisms of arthritis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>Iron deficiency, inflammation</td>
</tr>
<tr>
<td>Thromboembolic events</td>
<td>Hypercoagulopathies, platelet activation</td>
</tr>
<tr>
<td>Osteopathy</td>
<td>Steroid therapy, vitamin D deficiency inflammation</td>
</tr>
<tr>
<td>Growth failure</td>
<td>Malnutrition</td>
</tr>
<tr>
<td>Nephrolithiasis</td>
<td>Dehydration, hyperoxaluria, low urinary PH</td>
</tr>
<tr>
<td>Cholelithiasis</td>
<td>Intestinal loss of bile acids</td>
</tr>
<tr>
<td>Amyloidosis</td>
<td>Acute phase reaction, chronic inflammation</td>
</tr>
<tr>
<td>Fatty liver</td>
<td>Malnutrition</td>
</tr>
</tbody>
</table>

**Table 4** Drugs and their possible adverse side effects

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Possible adverse side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corticosteroids</td>
<td>Acne, fluid retention, fat redistribution, hypertension, hyperglycemia, psycho-neurological disturbances, cataracts, growth failure in children, osteonecrosis[^115]</td>
</tr>
<tr>
<td>Mesalazine</td>
<td>Nausea, dyspepsia, rare nephritis, rare idiosyncratic worsening of IBD[^116]</td>
</tr>
<tr>
<td>Sulfapyridine</td>
<td>Headache, nausea, anorexia, rare hypersensitivity hepatitis, hemolytic anemia, pancreatitis, reversible sperm abnormalities, worsening of IBD[^116]</td>
</tr>
<tr>
<td>Azathioprine/mercaptopurine</td>
<td>Pancreatitis, bone marrow suppression, hepatotoxicity[^115]</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>Nausea, leukopenia, hepatic fibrosis, hypersensitivity pneumonia[^117]</td>
</tr>
<tr>
<td>Cyclosporin</td>
<td>Nephrotoxicity, hypertension, headache, gingival hyperplasia, paresthesias[^118]</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>Nephrotoxicity[^115]</td>
</tr>
<tr>
<td>Infliximab</td>
<td>Infusion reactions, delayed hypersensitivity-like reactions, drug-induced lupus, tuberculosis reactivation[^119]</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>Nausea, metallic taste, peripheral neuropathy[^119]</td>
</tr>
</tbody>
</table>

Danese et al, 2005.
## DIAGNOSIS

<table>
<thead>
<tr>
<th>Early biomarker testing</th>
<th>IBD First Step</th>
<th>IBD Serology 7</th>
<th>IBD sgi Diagnostic</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASCA</td>
<td>ASCA- IgA</td>
<td>ASCA-IgA</td>
<td>STAT3</td>
</tr>
<tr>
<td>pANCA</td>
<td>ASCA-IgG</td>
<td>ASCA-IgG</td>
<td>ECM1</td>
</tr>
<tr>
<td>Anti-OmpC</td>
<td>ANCA-IgG</td>
<td>ANCA-IgG</td>
<td>NKX2.3</td>
</tr>
<tr>
<td>Anti-CBir1-IgA</td>
<td>ANCA</td>
<td>pANCA</td>
<td>ATG16L1</td>
</tr>
<tr>
<td>ANCA-IgG</td>
<td>Anti-OpmpC-IgA</td>
<td>DNase-sensitive</td>
<td>VEGF</td>
</tr>
<tr>
<td>pANCA</td>
<td>Anti-CBir1</td>
<td>pANCA</td>
<td>ICAM</td>
</tr>
<tr>
<td>Anti-OmpC</td>
<td>Anti-OmpC</td>
<td>ANTI-A4-Fla2</td>
<td>VCAM</td>
</tr>
<tr>
<td>Anti-Fla-X</td>
<td>Anti-Fla-X</td>
<td>ANTI-A4-Fla2</td>
<td>CRP</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DNase-sensitive</td>
<td>SAA</td>
</tr>
</tbody>
</table>
Treatment of IBD

1. 5-amino salicylic acid compounds (5-ASA)
   - Mesalamine based oral or topical
2. Glucocorticoids
3. Immunomodulators
4. Biological therapy (TNF-α inhibitors)
5. Surgery
5-amino salicylic acid compounds (5-ASA)
Aminosalicylates

- Topical anti-inflammatory drugs,
- 5-ASA has anti-inflammatory action due to:
  - inhibition of prostaglandins and leukotrienes
  - decrease neutrophil chemotaxis
  - antioxidant activity (scavenging free radical production)
- 5-ASA itself is absorbed from small intestine so pharmacokinetics / pharmaceutics matter
- Different formulations are used to overcome rapid absorption of 5-ASA from the proximal small intestine

- Sulfasalazine (Azulfidine)
- Mesalamine (Asacol, Pentasa, Lialda, Apriso, Delzicol)
  - Balsalazide (Colazal) Olsalazine (Dipentum)
- Rowasa enema, Canasa suppository
**Antiinflammatory Role**

- Mesalazine **inhibits** the enzymatic activity of Cyclooxygenase, Lipoxygenase, and PAF synthesis.

**Diagram:**
- **Cell Membrane Phospholipids**
  - Phospholipase A<sub>2</sub>
    - **Platelet Activating Factor**
    - **Arachidonic Acid**
      - Lipoxigenase
      - Cyclooxygenase

- **Leukotrienes** (LTB<sub>4</sub>)
- Lipoxins

- **Prostaglandins** (PGE<sub>2</sub>)
- Thromboxane
- Prostacyclin
**Sulfasalazine (Azulfidine)**

- Pro-drug combination of 5-ASA and sulfapyridine
- Is given orally, little amount is absorbed (10%)
- In the terminal ileum and colon, sulfasalazine is broken by azoreductase into: 5-ASA (not absorbed, active moiety) and Sulfapyridine (absorbed, side effects)
- Acetylator status matters with ADRs
- Idiosyncratic: SJS, TEN, DI Lupus, Hepatitis
- Dose dependent: Crystalluria, Bone marrow depression, Meagloblastic anemia, Folic acid deficiency, Oligospermia
Slow Acetylator Phenotype

- 50% of caucasians and african-americans have altered hepatic Phase II drug metabolism due to missing isoform of N-acetylation enzyme NAT-2.

- This “slow acetylation” phenotype implies decreased sulfapyridine clearance. So what?
Mesalamaine Compounds

Compounds that contain 5-ASA and connected by the azo bond ($\text{N} = \text{N}$) to sulfapyridine moiety, another molecule of 5-ASA or to inert compound.

- Sulfa free, well tolerated, have less side effects, and useful in patients sensitive or allergic to sulfa drugs

**Sulfasalazine**: 5-ASA + sulfapyridine (Azulfidine)

**Olsalazine**: 5-ASA + 5-ASA (Dipentum)

**Balsalazide**: 5-ASA + inert carrier (Colazal)

**pH / extended release**: Asacol, Lialda, Delzicol, Apriso

**Sustained release**: Pentasa
5-ASA Site of Release per Design of Various Delivery Systems

The information on this slide is not intended to compare the efficacy or safety of these products.

SAFETY
CONSIDERATIONS OF 5-ASA AGENTS

• Nephrotoxicity
  – Nephrotoxicity rate 0.26% per patient-year\(^1\)
  – Most often reported within the first 12 months of therapy\(^1\)
  – May be idiosyncratic rather than dose-related\(^1\)
  – Caution recommended when used in patients with known (or history of) renal disease\(^2,3\)
  – FDA recommends monitoring BUN/serum creatinine
  – Timely recognition of renal impairment and prompt discontinuation of 5-ASA in affected patients is important\(^1\)

• Pregnancy / breastfeeding
  – Safety in pregnancy demonstrated in several trials
  – Milk: serum ratios considered acceptably low
  – Considered safe for use in pregnancy and breastfeeding when indicated

Glucocorticoids

**Prednisone, prednisolone (orally)**
- Higher rate of absorption
- More adverse effects compared to rectal administration

**Hydrocortisone (enema or suppository):**
- Less absorption rate than oral.
- Minimal side effects & Maximum tissue effects

- Induction of remission in moderate & severe active IBD
- Not used for maintaining remission
- Oral glucocorticoids is commonly used in active condition
- Rectal glucocorticoids are preferred in IBD involving rectum or sigmoid colon
Budesonide

- A potent synthetic compound given orally (controlled release tablets) to release drug in ileum and colon
- Low oral bioavailability (10%)
- Is subject to first pass metabolism
- Used in treatment of active forms of moderate to severe UC & Crohn’s disease involving ileum and proximal colon
  - Potency 15x that of prednisolone
  - Delayed release capsule facilitates delivery to terminal ileum and proximal colon
  - Efficacy comparable to prednisolone with fewer side effects in adults with ileocecal Crohn's
  - Multinational paediatric study completed
  - 3 RCTs of oral budesonide 6mg/day, 3 mg/day and placebo
    - Budesonide 6mg/day ineffective at preventing relapse over 12 months.
      RR relapse = 0.89 (95% CI: 0.71-1.13)
      - Similar results with 3mg/day
Immunomodulators

Used to induce remission in IBD in active, severe conditions or steroid resistant patients.

Immunomodulators include:

- **Azathiporine, 6-mercaptopurine**
- **Methotrexate**
- **Cyclosporine**
- **Tacrolimus**
Purine Analogs
Azathioprine & 6-mercaptopurine

Azathioprine (Imuran)
- is a pro-drug of 6-mercaptopurine
- Inhibits purine synthesis
- Induction and maintenance of remission in IBD

TPMT testing (thiopurine methyltransferase)
- Homozygous deficiency (rare <1%)
- Heterozygous deficiency (50% activity)

Bone marrow depression: leukopenia, thrombocytopenia
Gastrointestinal toxicity
Pancreatitis
Hepatic dysfunction
CBC & liver enzymes are required in all patient
Azathioprine or 6-Mercaptopurine for inducing remission of Crohn’s disease

- 8 placebo controlled RCTs identified
- OR (95% CI) of response to AZA / 6-MP in active CD = 2.36 (1.57-3.53), NNT = 5,
  OR (95% CI) for steroid sparing effect = 3.86 (2.14-6.96), NNT = 3
- OR (95% CI) for adverse event (allergy, leukopenia, pancreatitis, nausea) = 3.01 (1.30-6.96), NNH = 14
- Azathioprine & 6-MP are effective at inducing remission in active Crohn’s disease.
Azathioprine for maintenance of remission in Crohn's disease
Pearson DC et al, Cochrane Review 1998

- 5 placebo controlled DBRCTs identified
- OR (95% CI) for maintenance of remission = 2.16 (1.4-3.5), NNT = 7
- Higher dose improved response (OR = 1.2 at 1mg/kg/day, 3.2 at 2mg/kg/day & 4.1 at 2.5mg/kg/day)
- OR for steroid sparing effect = 5.22 (1.1-25.7), NNT = 3
- OR for withdrawal due to adverse events = 4.36 (1.6-11.7)
LYMPHOMA & 6-MP/AZA

• 4-fold increased risk of lymphoma in IBD patients on IMD¹
• “Before putting the brakes on 6MP/AZA” a closer look at the data reveals²:
  1. Heterogeneity of the studies on the meta-analysis
  2. More severe IBD may raise the risk of lymphoma
  3. Weigh Risk (if any) versus benefit

USE OF IMMUNOSUPPRESSANTS: HIGHER INCIDENCE OF ABNORMAL PAP SMEARS IN WOMEN WITH IBD

Any abnormal pap Hx (%)

<table>
<thead>
<tr>
<th></th>
<th>Exposed</th>
<th>Non-exposed</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exposed to any immunosuppressant</td>
<td>63.0</td>
<td>33.3</td>
<td>14.6</td>
</tr>
<tr>
<td>OR 3.1 (1.4–6.5); p=0.005</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

p=0.01 exposed aza/6-MP

<table>
<thead>
<tr>
<th></th>
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<th>Control</th>
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</tr>
<tr>
<td>OR 3.1 (1.4–6.5); p=0.005</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Women >1 abnormal pap (%)

<table>
<thead>
<tr>
<th></th>
<th>Exposed</th>
<th>Non-exposed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exposed to aza/6-MP</td>
<td>44.6</td>
<td>22.0</td>
</tr>
<tr>
<td>OR 2.9 (1.2-4.1); p=0.02</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Conclusions:

- Women with IBD carry a higher risk for clinically important cervical lesions than healthy controls
- The effect of immunomodulator use increases this risk
- Women with IBD are appropriate candidates for inclusion under ACOG guidelines for increased cancer screening

Kane S, et al. DDW 2006, Los Angeles. Abstract #16
Methotrexate

- Folic acid antagonist - Inhibits dihydrofolate reductase required for folic acid activation
- Orally, S.C., I.M.
- Used to induce and maintain remission in inflammatory bowel diseases.

- Bone marrow depression
- Megaloblastic anemia
ANTI-TNF AGENTS

- **Infliximab** *(Remicade)* 1999 UC & CD
- **Adalimumab** *(Humira)* 2002 UC & CD
- **Natalizumab** *(Tysabri)* 2006 CD
- **Certolizumab pegol** *(Cimzia)* 2008 CD
- **Golimumab** *(Simponi)* 2009 UC
- **Vetolizumab** *(Entyvio)* 2014 UC & CD

### Table: Anti-TNF Agents

<table>
<thead>
<tr>
<th></th>
<th>Infliximab</th>
<th>Adalimumab</th>
<th>Certolizumab</th>
<th>Natalizumab</th>
<th>Ustekinumab</th>
<th>Golimumab</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Approved indications</strong></td>
<td>UC RA PsA AS</td>
<td>CD UC RA PsA AS JRA Psoriasis</td>
<td>CD RA</td>
<td>CD MS</td>
<td>Psoriasis Phase II/III studies for CD</td>
<td>RA PsA AS Phase II/III studies for UC</td>
</tr>
<tr>
<td><strong>Structure</strong></td>
<td>Chimeric IgG1 κ</td>
<td>Human IgG1 κ</td>
<td>Humanized pegylated Fab IgG4</td>
<td>Humanized IgG4</td>
<td>Human IgG1 κ</td>
<td>Human IgG1 κ</td>
</tr>
<tr>
<td><strong>Therapeutic target</strong></td>
<td>TNF-α</td>
<td>TNF-α</td>
<td>TNF-α</td>
<td>α4 integrin</td>
<td>IL-12/23 (p40 subunit)</td>
<td>TNF-α</td>
</tr>
<tr>
<td><strong>Dosage in IBD</strong></td>
<td>5 mg/kg 0-2-6 and every 8 wk</td>
<td>160-80-40 mg/2 wk and every 40 mg eow</td>
<td>400 mg 0-2-4 wk and every 4 wk</td>
<td>300 mg every 4 wk</td>
<td>45 mg at baseline, 4 wk after, and every 12 wk thereafter (90 mg if weight &gt; 100 kg)</td>
<td>50 mg monthly</td>
</tr>
<tr>
<td><strong>Administration route</strong></td>
<td>i.v.</td>
<td>s.c.</td>
<td>s.c.</td>
<td>i.v.</td>
<td>s.c.</td>
<td>s.c.</td>
</tr>
<tr>
<td><strong>Brand name</strong></td>
<td>Remicade</td>
<td>Humira</td>
<td>Cimzia</td>
<td>Tysabri</td>
<td>Stelara</td>
<td>Simponi</td>
</tr>
</tbody>
</table>

AS, ankylosing spondylitis; CD, Crohn’s disease; eow, every other week; Fab, antigen-binding region; IBD, inflammatory bowel disease; IgG, immunoglobulin G; IL, interleukin; i.v., intravenous; JRA, juvenile rheumatoid arthritis; mAbs, monoclonal antibodies; MS, multiple sclerosis; PsA, psoriatic arthritis; RA, rheumatoid arthritis; s.c., subcutaneous; TNF-α, tumor necrosis factor-α; UC, ulcerative colitis; wk, weeks.
INFLIXIMAB (REMICADE)

- Chimeric IgG monoclonal antibody to TNF-α
- infliximab is TNFα inhibitor
- It binds to TNFα, preventing it from activating TNF receptors
- Has an advantage that it is given SC and is approved for treatment of moderate to severe Crohn’s disease, rheumatoid arthritis, psoriasis.

**5 mg/kg**
- given at 0, 2, and 6 weeks as an induction regimen

**5 mg/kg**
- every 8 weeks thereafter as a maintenance regimen

**IF RESPONSE WAS LOST, REGAIN RESPONSE WITH**

**10 mg/kg**
- (36/40) of patients treated with REMICADE® 5 mg/kg regained response with an increased dose²³

Mouse protein

Human IgG1
ADALIMUMAB (HUMIRA)

- Fully humanized IgG antibody to TNF-α
- Adalimumab is TNFα inhibitor
- It binds to TNFα, preventing it from activating TNF receptors
- Has an advantage that it is given SC and is approved for treatment of moderate to severe Crohn’s disease, rheumatoid arthritis, psoriasis.
Anti-TNF Side effects

- Acute or early adverse infusion reactions
  - allergic reactions or anaphylaxis in 10% of patients
- Delayed infusion reaction
  - serum sickness-like reaction, 5% of patients
- Pretreatment with diphenhydramine, acetaminophen, corticosteroids is recommended
- Infection complications
  - Latent tuberculosis, sepsis, hepatitis B
- Loss of response to infliximab over time due to the development of antibodies
- Severe hepatic failure
- Rare risk of lymphoma
Rationale for Monitoring IBD Patients Treated with Anti-TNFs

- ~150,000 IBD patients are currently on anti-TNFs
- ~50% of IBD patients will require dose modification or switch to another treatment\(^1\)
- Many patients with IBD who have symptoms may not have active inflammation
- Monitoring strategies that identify patients who have insufficient drug, anti-drug antibodies, or patients whose symptoms are due to causes other than active IBD may help guide treatment outcomes for individual patients

Alzafiri et al. Clinical and Experimental Gastroenterology 2011; (4):9-17
1. Knowing what factors are contributing to a patient’s loss of response to a biologic may be helpful for determining an appropriate course of action:

2. Empiric strategy may lead to intensification of treatment in patients:
   - who are antibody positive and may have obtained a greater benefit by switching to another agent
   - who have therapeutic levels of drug and no antibodies where TNF may not play a major role in the maintenance of inflammation
   - who have symptoms that could be due to alternate etiologies
Detectable Serum Trough IFX Concentration is Associated with Higher Remission Rate and Endoscopic Improvement in UC Patients

- Study design: cohort study
- n=115 with moderate to severe UC
- Follow-up time: median 13.9 mo
- Efficacy
  - Detectable serum IFX was associated with
    - Higher remission rates (69% vs. 15%; P<0.001)
    - Endoscopic improvement (76% vs. 28%; P<0.001)
  - Undetectable serum IFX predicted an increased risk for colectomy (55% vs 7%; p<0.001)

Seow CH et al. Gut 2010;59:49-54
Measuring Infliximab and ATI Concentrations

In a retrospective analysis of 155 CD patients measuring IFX and ATI impacted treatment decisions in 73% of the clinical situations.

Subtherapeutic IFX concentration defined as ≤12 mcg/ml at 4 wks or undetectable at trough.

Published Treatment Algorithm in IBD: Patients With Loss of Response

**Positive ATI**
- Consider change to another anti-TNF agent
- **persistent disease**
- Consider change to non-anti-TNF agent

**Negative ATI**
- Therapeutic IFX concentration
  - Active disease on endoscopy/radiology?
    - **yes**
      - Consider change to non-anti-TNF agent
    - **no**
      - Consider investigating alternate etiologies

**Subtherapeutic IFX concentration**
- Consider inc. infliximab dose or frequency
- Consider change to different anti-TNF agent
- Consider change to non-anti-TNF agent

Yanai et al. *Am J Gastroenterology* 2010; 106: 685-698

CONFIDENTIAL
Serum ADA and ATA Levels Correlate Well with Disease Activity

- N=66 IBD Patients (59 CD, 7 UC) with a cross-Sectional study design

- Detectable ATA was associated with:
  - ADA < 5µg/mL (p<0.001)
  - Mucosal inflammation (p=0.03)
  - Need for steroids (p=0.03)
  - Previous IFX use (p=0.04)

- ADA concentration of < 5 µg/mL predicted elevation in CRP in ATA negative samples

- Mean CRP levels were significantly higher in ATA+ vs. ATA- (12 vs. 2.1 mg/L, p=0.002)
CONSIDER THIS....

• Let the disease dictate therapy options
• Best options may not be possible – cost & compliance concerns
• Disease education essential
• Weigh risks versus benefits, Top-down therapy likely best
• If you do it, do it right! Testing & compliance
Thank you!

Questions?