In my lecture today, I will be discussing off label use of several medications to treat Crohn's disease.
Thomas

- 21 year old male with a 4 year history of extensive small bowel CD treated with infliximab for the past 3 years presents with increasing cramping abdominal pain, 12 pound weight loss and diarrhea
- No recent travel or antibiotics
- No previous abdominal surgery
- SH: Does not smoke
- FH: No FH of IBD
- On infliximab 10mg/kg q 6 wk

PE shows a well appearing male in NAD with fullness in the RLQ
- Stool samples for enteric pathogens and C. diff negative
- CTE/MRE- long segment of bowel wall thickening with associated inflammatory changes in mid jejunum and terminal ileum
- IFX level nondetectable (trough < 1.4 mcg/ml)
- ATI positive

<table>
<thead>
<tr>
<th>Labs</th>
<th>WBC 11.5K</th>
<th>Hct 31%</th>
<th>MCV 82</th>
<th>Platelets 435K</th>
<th>CRP 9.5 mg/dl (nl &lt;1.0)</th>
</tr>
</thead>
</table>
1. Discontinue infliximab and add antimetabolite (AZA/6MP/MTX) if not previously taken
2. Increase infliximab dose or change interval
3. Switch to adalimumab or certolizumab
4. Switch to natalizumab

Crohn’s Disease
How to Assess Efficacy of Biologic Therapy and When to Switch
Efficacy Endpoints

- **Clinical response**
  - CDAI decrease 70-100 points
- **Clinical remission**
  - CDA <150
- **Mucosal healing**
  - Absence of mucosal ulceration on colonoscopy
- **“Deep remission”**
  - Clinical remission plus mucosal healing

Other Efficacy Endpoints

- Maintenance of response/remission
- Elimination of steroids
- Healing of fistulae
- Reduction of hospitalization/surgeries
- Improvement in QOL
- Improvement in work productivity
- Decrease in CRP, stool calprotectin
Is There Active Inflammation?

• Assess for active luminal disease
• Exclude infections (C. diff, CMV, intra-abdominal abscess, small intestinal bacterial overgrowth)
• Exclude celiac, bile salt malabsorption, fistula, short gut
• Superimposed irritable bowel syndrome should be identified and treated appropriately
• Individuals with a fixed stenosis without active inflammation need surgery and not an anti-TNF

Assess Response to Rx

• Primary Nonresponders
  – Individuals who fail to respond to initial induction therapy within 12 weeks
• Secondary Nonresponders
  – Improve after initial induction but subsequently lose their response or become intolerant of their anti-TNF agent
Management of the Primary Nonresponder

- Approximately 35-40% of patients in anti-TNF clinical trials are primary nonresponders
- Assess for response at 8-12 weeks
- For primary nonresponders
  - Start antimetabolite (6MP/AZA/methotrexate) for patients not previously on these agents
  - Switch to second anti-TNF
  - Switch to natalizumab
  - Surgery may be an option to consider in patients with limited disease


Management of the Primary Nonresponder - Start Antimetabolite

- If not previously treated with an antimetabolite
  - Stop anti-TNF and begin monotherapy with antimetabolite
  - Add antimetabolite to anti TNF
Crohn’s Disease
Management of the Primary Nonresponder
Switch to Adalimumab or Natalizumab

• Adalimumab (Europe-CARE)
  – 945 patients treated with open label adalimumab (160mg/80mg)
    • Response and remission measured using Harvey Bradshaw Index
  – 94 patients/primary nonresponders to infliximab:
    • 28% achieved remission at week 4
    • 36% were in remission at week 20

ENCORE trial (n = 509) with moderate to severe Crohn’s disease and an elevated CRP were randomized to natalizumab 300mg IV given at 0, 4 and 8 weeks

In a subgroup analysis in these trials, there were no statistical differences in natalizumab treated patients who were primary nonresponders to infliximab and in those patients not exposed to infliximab


Crohn’s Disease
Management of Secondary Nonresponders

Increase Dose of Initial Anti-TNF
Management of Loss of Response to IFX: Measurement of IFX Levels and ATIs

- Mayo study of 155 patients who had antibodies to infliximab (ATI) and infliximab concentrations measured
- Testing performed in patients with loss of response to infliximab (49%), partial response after initiation of infliximab (22%), and possible autoimmune delayed hypersensitivity reaction (10%)
- ATIs were identified in 35 patients (23%) and therapeutic infliximab concentrations in 51 patients (33%)

Measurement of IFX Levels and ATIs

Test results impacted treatment in 73% of patients

<table>
<thead>
<tr>
<th>Subtherapeutic IFX</th>
<th>Dose escalation</th>
<th>Complete or partial response - 86%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subtherapeutic IFX</td>
<td>Switch anti-TNF</td>
<td>Response - 33%</td>
</tr>
<tr>
<td>Therapeutic IFX</td>
<td></td>
<td>No evidence of active inflammation in 62% of the patients</td>
</tr>
<tr>
<td>ATIs + patients</td>
<td>Switch anti-TNF</td>
<td>Response - 92%</td>
</tr>
<tr>
<td>ATIs + patients</td>
<td>Dose escalation</td>
<td>Response - 17%</td>
</tr>
</tbody>
</table>

“Increasing the infliximab dose in patients who have HACAs is ineffective, whereas in patients with subtherapeutic infliximab concentrations, this strategy may be a good alternative to changing to another anti-TNF agent.”
Management of Loss of Response to the First Anti-TNF Agent: Adalimumab

Adalimumab-CHARM trial (854 patients)

- 260 patients who responded to open label induction therapy, randomized to adalimumab every other week (EOW)
- 140 (54%) continued blinded EOW therapy and 120 (46%) moved to open label therapy for flare or nonresponse
- Among open label cohort, 49 (19%) continued EOW therapy and 71 (27%) moved to weekly therapy


Management of Loss of Response to the First Anti-TNF Agent: Certolizumab

PRECiSE 4 (ongoing open-label extension trial)

- Patients on continuous therapy underwent recapture with a single extra 400-mg dose of certolizumab
  - PRECISe 2 pts who relapsed before week 26 could enter PRECISe 4
  - Disease activity measured by Harvey-Bradshaw Index
- Week 4 Response Rates: 63% in pts who relapsed on continuous therapy; 65% after drug interruption
- Response was maintained in 55% and 59% of these responders, respectively, through week 52

Crohn’s Disease
Management of Secondary Nonresponders
Switch Anti-TNF agent

Secondary Nonresponder
Switch from Infliximab to Adalimumab

GAIN Trial

- 325 adults 18-75 years of age with moderate to severe CD (CDAI score, 220-450 points) and who lost response to infliximab or had adverse events
  - Randomly assigned to induction doses of adalimumab (160 mg/80 mg) or placebo at weeks 0 and 2
  - 301 completers
- Week 4: 21% (34 of 159) in adalimumab group vs 7% (12 of 166) in placebo group achieved remission
- Week 4: 70-point response in 52% (82 of 159) in adalimumab group vs 34% (56 of 166) placebo group

GAIN: Clinical Response and Remission to Adalimumab

In Patients with Moderate to Severe CD and Secondary Failure to Infliximab

![Graph](image)

**Response (CR70)**
- Placebo: 34%
- Adalimumab 160/80 mg EOW, SC: 52%

**Response (CR100)**
- Placebo: 24%
- Adalimumab 160/80 mg EOW, SC: 38%

**Remission CDAI ≤150**
- Placebo: 7%
- Adalimumab 160/80 mg EOW, SC: 21%

***p<0.001, **p<0.01, both vs placebo

Full analysis population


Secondary Nonresponder: Switching from Infliximab to Certolizumab

WELCOME Trial

- 26 week study: 539 patients with active CD and secondary failure to infliximab received open-label induction with certolizumab 400 mg at weeks 0, 2, 4
- Responders randomized to certolizumab 400 mg every 2 or every 4 weeks through week 24
- Primary end point was response at week 6 and secondary end points included remission at week 6 and response and remission at week 26
- Week 6: 334 of 539 patients (62.0%) achieved response and 212 of 539 (39.3%) achieved remission

Certolizumab in Patients with Moderate to Severe CD and Secondary Failure to Infliximab

WELCOME Trial Response and Remission Rates

(A) over the open-label induction phase (n = 539)

(B) at week 26 (n = 329)


Secondary Nonresponder Switching to a Third Anti-TNF

- Open label study of the use of certolizumab or adalimumab after failure and/or intolerance to two different anti-TNF agents
- Sixty-seven patients treated with certolizumab (n = 40) or adalimumab (n = 27) were included
  - Clinical response observed in 41 patients (61%) at week 6 and 34 patients (51%) at week 20
  - Probability of remaining on treatment at 3, 6 and 9 months was 68%, 60% and 45%, respectively
  - At end of follow-up, third anti-TNF stopped in 36 patients for intolerance (n = 13), or failure (n = 23)
  - Two deaths observed (sudden death and line sepsis)

Summary

• Document active inflammation before beginning treatment with an anti-TNF, escalating the dose or switching to another anti-TNF or natalizumab

• Infections including C. diff, CMV, intra-abdominal abscess and bacterial overgrowth need to be excluded

• Wait 8-10 weeks after starting treatment with an anti-TNF agent to assess response to therapy

Summary

• Active CD and primary nonresponder to an anti-TNF
  – Add antimetabolite if not previously taken
  – Use a second anti-TNF
  – Switch class and use natalizumab

• Active CD in secondary nonresponder
  – Measurement of drug levels/antibodies (if available) or dose escalation before switching to a second anti-TNF
Summary

• Active disease in secondary nonresponder
  – Switch to a second anti-TNF
  – Switch class and use natalizumab

• Individuals with stenosing disease without active inflammation should be referred for surgical consultation

Thomas: Follow-up

• Breath test for bacterial overgrowth negative
• Received appropriate vaccinations
• Infliximab stopped and induction dose of second anti-TNF administered with patient entering remission
• Antimetabolite 6MP added at 50mg a day
• Patient well 9 months after switch
Thomas: Scenario 2

- 21 year old male with a 4 year history of extensive small bowel CD treated with infliximab for the past 3 years presents with increasing cramping abdominal pain, 12 pound weight loss and diarrhea
- No recent travel or antibiotics
- No previous abdominal surgery
- SH: Does not smoke
- FH: No FH of IBD
- On infliximab 10mg/kg q 6 wk

Thomas: Scenario 2

- PE shows a well appearing male in NAD with fullness in the RLQ
- Stool samples for enteric pathogens and C. diff negative
- MRE- 5cm segment of small bowel disease with small bowel dilation proximal to the area of involvement but w/o inflammation
- IFX level (trough: 8.0 mcg/ml)
- ATI negative

Labs

<p>| | |</p>
<table>
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<tr>
<td>CRP</td>
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**Thomas: Treatment Options**

1. Increase infliximab dose or shorten interval
2. Add an antimetabolite (AZA/6MP/MTX) and continue infliximab
3. Switch to adalimumab or certolizumab pegol
4. Switch to natalizumab
5. Continue infliximab but evaluate for small bowel intestinal overgrowth, irritable bowel syndrome, bile salt malabsorption, etc
6. Send for ileocecectomy

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**Thomas: Follow-up Scenario 2**

- Therapeutic infliximab levels and short segment of fixed non-inflammatory disease
- No evidence for bacterial overgrowth
- Send for surgery and laparoscopic ileocecectomy performed
- Treated postop with metronidazole 500mg po bid for 3 months as well as 6MP
- Doing well 10 months postop with colonoscopy demonstrating 2 isolated aphthous erosions in the neoterminal ileum
Crohn’s Disease
Minimizing Side Effects of Steroids, Antimetabolite and Biologic Agents

Corticosteroid Toxicity

- Moon face
- Acne
- Ecchymoses
- Hypertension
- Hirsutism
- Petechial bleeding
- Striae
- Diabetes
- Infection
- Osteonecrosis
- Osteoporosis
- Myopathy
- Cataracts
- Glaucoma
- Psychosis
Minimizing Steroid Toxicity

- Assess for risk factors for osteoporosis and perform DEXA if appropriate
- Supplement Vitamin D, calcium daily
  - 1200 mg Calcium
  - 800 IU vitamin D
- Monitor fasting glucose levels
- Have an exit strategy for steroid use

Azathioprine/6-Mercaptopurine Toxicity

- Nausea
- Allergic reactions (fevers, arthralgias)
- Pancreatitis
- Bone marrow depression
- Drug-induced hepatitis
- Infectious complications
- Lymphoma, non-melanoma skin cancer
Lymphoma Risk and Thiopurines

- CESAME cohort
  - 19,486 patients in France with IBD
  - Outcomes based on drug exposure
- 23 new cases of lymphoproliferative disorders diagnosed
- HR 5.28 (2.01-13.9) for lymphoproliferative disorder with thiopurine exposure


Minimizing Toxicity from Thiopurines

- Check TPMT first to rule out those with low enzyme activity
- Schedule regular CBC, liver enzymes
- Educate patient on symptoms to watch for
- Dosing at night anecdotally alleviates some complaints of nausea
- Vaccinate patients for age-appropriate diseases prior to initiation

### General Vaccination Considerations in the IBD Patient

**Titers to check at first office visit:**

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Requirement</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMR</td>
<td>If vaccination history unknown</td>
</tr>
<tr>
<td>Varicella</td>
<td>If vaccination history or history of chicken pox/zoster unknown</td>
</tr>
<tr>
<td>Hepatitis A</td>
<td>Except those with evidence of protective titer within 5 years of vaccine administration</td>
</tr>
<tr>
<td>Hepatitis B</td>
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</tr>
</tbody>
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**Vaccinations to consider if NO plans to start immunosuppressive therapy in 4-12 weeks:**

<table>
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<tr>
<td>Tdap</td>
<td>Hepatitis A</td>
</tr>
<tr>
<td>HPV</td>
<td>Hepatitis B</td>
</tr>
<tr>
<td>Influenza</td>
<td>Meningococcal</td>
</tr>
<tr>
<td>Pneumococcal</td>
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</table>

**Vaccinations to administer in specific patient groups regardless of immunosuppressive drug use:**

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### Methotrexate Toxicity

- Rash
- Nausea, mucositis, diarrhea
- Bone marrow suppression
- Hypersensitivity pneumonitis
- Increased liver enzymes
- Hepatic fibrosis/cirrhosis
- Known abortifacient
- No documented increased risk of lymphoma or skin cancer

---

Minimizing Methotrexate Toxicity

- Regular counseling regarding birth control
- 1 mg Folic acid supplementation daily
- Monitor CBC, liver enzymes monthly
- Evaluate risk factors for liver disease
  - Diabetes
  - Obesity
  - Alcohol abuse
- Liver biopsy no longer recommended


Anti-TNF Agents: Adverse Events

- Immunogenicity
- Infection
  - Granulomatous (TB, histo, *Listeria*)
  - Viral, fungal
- Autoimmunity
- Lymphoproliferative dx?
- Neoplasm
  - Skin
  - Pediatric tumors
- Psoriasis lesions
- Demyelinating disorders true causal ???
- Worsen or de novo congestive heart failure
- Hepatotoxicity (rare) true causal??

Minimizing Toxicity for Anti-TNF Therapy

- Rule out evidence for TB prior to initiation
  - If immunocompromised, PPD and Quantiferon may be negative
- Rule out active infection prior to initiation
  - Abscess
  - C difficile
  - CMV
- Vaccination for age-appropriate diseases


Minimizing Toxicity for Anti-TNF Therapy

- Check serologies for Hepatitis B
- Assess for signs/symptoms of:
  - Uncontrolled heart failure
  - Demyelinating disorders (MS)
  - Skin cancers/suspicious moles

Natalizumab

- As of August 2011
  - 150 cases of JC virus related progressive multifocal leukoencephalopathy (PML)
  - ~ 88,100 pts have received natalizumab
  - > 38,700 pts have been treated for longer than 2 years

- As of 5/2011, there has been one postmarketing case of PML in a Crohn’s patient in addition to one case in clinical trials
- All PML cases after 1 year of natalizumab therapy
- Risk increases with duration of treatment
- Rate approximately 1.66 per 1000 treated patients


Natalizumab: TOUCH

- Risk minimization program
- Infusion centers and prescribing MDs must be registered
- No concomitant antimetabolites
- Discontinue natalizumab if no response after 3 months of treatment
- Discontinue natalizumab if unable to discontinue steroids by six months
- Patients quizzed about neurologic symptoms at each infusion
- JC virus antibody test became available September 2011 through Quest and Elan (Quest: 90257, JC Virus Antibody with Reflex to Inhibition Assay)
Summary Safety Slide

- Corticosteroids appear to be associated with many adverse events and side effects
- Patients on antimetabolites need to be monitored for short and long term side effects
- Biologics can cause immune as well as infectious type of complications
- JC virus antibody test now available through Quest and Elan (Quest: 90257, JC Virus Antibody with Reflex to Inhibition Assay)
- Balance risk and benefit for each patient