Current and Future Medical Therapy in Inflammatory Bowel Disease
Talk outline

• Review of benefits and risks of different medication classes
• Recent advances in IBD
Medical therapy in IBD

• Currently there is no cure for Crohn’s
• The only cure for ulcerative colitis is taking out the colon
• All but the patients with the mildest of disease will need to be on chronic lifelong therapy
• Goals of therapy –
  – Induce and maintain a clinical remission
  – Avoid complications of the disease
  – Achieve a good quality of life
  – Minimize short and long term toxicity
Medications in IBD – Benefits and Risks
Medication Classes

- 5-aminosalicylic acid agents
- Steroids
- Thiopurines
- Anti-TNF agents
- Natalizumab
FDA approval table

- **Crohn’s disease** –
  - Induction – mild to moderate
    - budesonide
  - Induction and maintenance – moderate to severe
    - infliximab, adalimumab, certolizumab pegol, natalizumab

- **UC** –
  - Induction – mild to moderate
    - budesonide MMX
  - Induction and maintenance – mild to mod
    - 5-aminosalicylic acid
  - Induction and maintenance - mod to severe
    - infliximab, adalimumab, simponi
5-aminosalicylic acid (5-ASA)—benefits

- Effective for induction and maintenance of remission of mild to moderate ulcerative colitis
- Comes in several forms – Azulfidine, Asacol, Lialda, Pentasa, Apriso
- Often combination therapy with rectal 5-ASA (Rowasa, Canasa) works better than oral alone
  - For proctitis, can treat with topical 5-ASA alone
- Probably a role for Pentasa with mild Crohn’s, but probably not more severe disease
5-aminosalicylic acid - **risks**

- Generally very safe and well tolerated
  - With some formulations need to take up to 12 pills a day
- A minority of patients will actually get worse on this class of medications
- Need to check kidney function (blood test) once a year
Corticosteroids - benefits

- Effective in the induction, but not maintenance of remission in both Crohn’s and UC
- Most common formulations are Prednisone and Entocort
- In UC, usually used with active flares when 5-ASAs are not working
  - Usually involves starting prednisone at 40mg a day, and taper over 8 – 10 weeks
- In Crohn’s involving the small intestines and right colon (most common locations), Entocort is preferred over prednisone
Corticosteroids - risks

• The long-term risks of steroids are significant:
  – Diabetes
  – High blood pressure
  – Increased risk of infection
  – Osteopenia and osteoporosis
  – Avascular necrosis of the hip
  – Water retention / weight gain
  – Cataracts
  – Skin thinning / bruising
  – Hormonal imbalance
  – Anger, anxiety or other psychiatric effects
Corticosteroids - risks

- Overall, 55% of patients on corticosteroids will have an adverse event and will have to discontinue therapy.
- Historically, Crohn’s patients on corticosteroids have a high likelihood of becoming steroid dependent or requiring surgery.
- Long-term treatment with steroids is inappropriate!!!
Thiopurines - benefits

- Steroid sparing oral agents
  - 2 medications – Imuran, 6-mercaptopurine
- Oral immunosuppressives – effective in maintaining remission in Crohn’s and UC in about 50% of patients
  - Usually started when 5-ASAs are not enough to control moderate to severe symptoms or for steroid dependence
  - No role for inducing a remission because it takes 2-4 months to become clinically active
- Usually combined with a steroid taper when it is started
Thiopurines - risks

- Potential reactions / adverse events
  - Low white blood cell count
  - Increased risk for infection
  - Increased risk for lymphoma
    - About 4-5 times over the general population
  - Elevated liver function tests
  - Pancreatitis (3%)
  - Allergic reaction
  - Fatigue
- Need close blood monitoring
  - Especially important when medication is first started
- Overall, about 10% of patients will need to stop the medication because of a reaction or adverse event
Effectively communicating risk of lymphoma
Anti-TNF agents
Anti-TNF agents - benefits

• Approved for induction and maintenance of remission for Crohn’s (infliximab, adalimumab, certolizumab pegol) and UC (infliximab, adalimumab, golimumab)
  – Usually started when 5-ASAs or thiopurines are not enough to control moderate to severe symptoms, or for steroid dependence
  – The most effective therapy available for perianal fistulizing disease
Anti-TNF agents - risks

- Potential reactions / adverse events
  - Immediate or delayed infusion or injection site reaction
  - Increased risk for infection
  - The risk of lymphoma is unknown
- Overall, about 10% of patients will have an adverse event, but only 1/250 events will be serious
  - Caution must be taken in combining these medications with steroids for an extended period
- Additionally, up to 50% of patients will lose response to an agent over time
  - Can switch to another anti-TNF, but usually not as effective as the first agent
Natalizumab - benefits

- Effective in inducing and maintaining remission in Crohn’s disease
  - Also effective therapy in multiple sclerosis
- Administered as a once monthly infusion
- Usually started in patients who have failed an anti-TNF agent and for whom surgery is not a good option
- Patients must be off all immunosuppressants other than steroids
Natalizumab - **risks**

- Potential reactions / adverse events
  - Progressive multifocal leukoencephalopathy (PML)
    - 1:1000 risk, fatal or debilitating if acquired
    - Need close monitoring with neurologic exams – TOUCH program
    - Major risk factors – JC virus positive, prior immunosuppressives, use greater than 24 months
    - If it does not work in the first 3 months, it is stopped
• Recent advances in IBD
  – Top-down vs. step-up therapy
  – Mucosal healing as a goal of treatment
  – When can immune based therapy be stopped
  – When is medical therapy futile
  – New and upcoming agents
1. Step-up vs. top-down therapy
Top-down therapy

- Most applicable to Crohn’s disease
- Refers to starting anti-TNF agent (often with a thiopurine agent)
  - New data emerging that combination therapy may be most effective early in the course of disease
  - The hope is this will decrease complication, hospitalization and surgery rates
- Need to weigh the benefits and risks of combination therapy
  - Important to understand at diagnosis who will have an aggressive course with complications and need for early surgery
  - In the future, we will be able to better predict on the basis of clinical, genetic, and laboratory factors
II. Mucosal healing as a goal of therapy

- Clearly the chief goal of therapy is to induce and maintain a clinical remission
- There is evidence that patients in clinical remission who also achieve “mucosal healing” are less likely to flare over time
  - Mucosal healing does not always correlate well with clinical symptoms
- Currently our medications do an overall poor job at achieving mucosal healing
- There is no clear consensus as to how we should strive to achieve mucosal healing as a goal of therapy
UC - Spectrum of Disease

Normal

Mild

Moderate

Severe
III. Using our medications smarter

- Sometimes it is difficult to determine how well a medication is working
  - Everyone is different
- 6-MP/azathioprine – can check levels of the active metabolite
- Infliximab – can check levels of infliximab as well as antibody levels
  - Very expensive test, even with insurance
III. When can anti-TNF or thiopurine therapy be safely stopped?

- In most cases, therapy cannot be safely stopped without a significant risk of relapse.
- In patients on an anti-TNF agent in combination with a thiopurine agent, a subset of patients probably can stop one of the medications.
  - In order to achieve this, patients should have clinical and endoscopic remission as well as have no elevated markers of inflammation.
  - We are only now learning which factors predict the ability to come off medication.
IV. When is medical therapy futile in IBD

- Sometimes medical therapy is inappropriate. Examples include:
  - A scarred down stricture that is best approached with surgery
  - Extensive fistulizing disease or abscess within the abdomen which needs surgery (followed by medical therapy)
  - Patients with no detectable active disease
V. New agents available

- Ulcerative colitis –
  - Budesonide MMX for induction of mild to moderate ulcerative colitis
  - Adalimumab for induction and maintenance of moderate to severe disease
  - Golimumab for induction and maintenance of moderate to severe disease

- Crohn’s – nothing recent
VI. New agents: in development

- **Ulcerative colitis** –
  - Vedolizumab – cousin of natalizumab
  - Does not affect the brain
  - Tofacitinib – oral agent – beginning Phase III study

- **Crohn’s disease** –
  - Ustekinumab – Phase III, finished enrolling
  - Vedolizumab