New advancements and treatment options in IBD
Talk outline

• Overview
• 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
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-ASA 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 and UC (Remicade and Humira only)
  – 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
  - Increased risk for infection
  - Progressive multifocal leukoencephalopathy (PML)
    - 1:1000 risk
    - Fatal or debilitating if acquired
    - Need close monitoring with neurologic exams
    - If it does not work in the first 3 months, it is stopped
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
Controversies in the field
Recent advances in IBD
I. Step-up vs. top-down therapy

Inflammatory Bowel Disease

Experimental Therapies
(II-10/IV Azathioprine)

Infliximab

Cyclosporine

Methotrexate

6-Mercaptopurine/ Azathioprine

IV Corticosteroids

Oral Corticosteroids

Antibiotics

5-ASA/Sulfasalazine

Topical 5-ASA

Aggressive

Most

Least

Therapeutic pyramid
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
- Remicade – can check levels of remicade as well as antibody levels
  - Very expensive test, even with insurance
IV. New agents available

- Ulcerative colitis —
  - Humira for induction and maintenance of moderate to severe disease
  - Uceris for induction of mild to moderate ulcerative colitis

- Crohn’s disease —
  - Sorry, nothing recent
New agents: in development

- **Ulcerative colitis** –
  - Vedolizumab – cousin of Tysabri
  - Tofacitinib – oral agent – beginning Phase III study
- **Crohn’s disease** –
  - Ustekinumab – Phase III, finished enrolling
  - High dose cytoxan – for severe disease
- **Other** –
  - Stool transplant in patients with recurrent C. difficile infection
2) 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 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
4) 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
Conclusions

• It is crucial that you have good communication with your gastroenterologist
• In many cases, the benefits of these medications do outweigh the risks
• As the patient, you should be confident that you and your doctor have appropriately weighed the pros and cons of therapy
More Conclusions

• It is very important that you take your medication as prescribed, even if you are feeling well
• Failure to do so can result in a flare of disease, and in some cases, the drug will not work as well in the future