• In my lecture today, I will be discussing off label use of several medications to treat Crohn’s disease
Nancy

- 30 year old female presents with 3 month history of perianal pain and drainage without change in stool habits
  - Treated empirically with metronidazole with only minimal improvement
  - Colonoscopy with TI intubation and biopsy show evidence of patchy colitis with rectal involvement c/w Crohn’s disease
- FH: positive for Crohn’s in brother
- PE: Normal except rectal exam which showed...
Cumulative Incidence of Crohn’s Fistulas

- Any fistula
- Perianal fistula


Frequency of Perianal Fistulas

- According to Anatomic Location of Bowel Involvement

- Colon only (without rectal involvement) 41%
- Small intestine only 12%
- Rectum only 92%
- Combined ileocolic involvement 15%

**Park’s Classification of Perianal Fistulas**

- Extrasphincteric
- Trans-sphincteric
- Superficial
- Intersphincteric
- Suprasphincteric
- External anal sphincter

**Simple vs Complex Fistula**

- Simple
- Complex

References:

Diagnostic Options Used in the Classification of Perianal CD

- History
- Physical Exam
- Imaging
  - Fistulography
  - CT
  - MRI
  - Endorectal ultrasound

What Happens When Fistulas are Missed at Time of EUA?

- 52% of patients needed repeat surgery in cases where surgery and MRI disagreed
- Fistula recurrence was always at site predicted by MRI

Does Controlling Fistula Healing Make a Difference?

N = 32

Fistula Recurrence

- Inflix Only: 79%
- EUA Before Inflix: 44%

Response to Treatment

- Inflix Only: 83%
- EUA Before Inflix: 100%

p=0.014
p=0.001


Setons Prevent Abscesses by Preventing Premature Closure of Fistula Tract

Medical Therapies

- Antibiotics (metronidazole, ciprofloxacin)
- Antimetabolites
  - Azathioprine
  - 6-mercaptopurine
  - Methotrexate
- Cyclosporine
- Tacrolimus
- Biologic Agents
  - Infliximab
  - Adalimumab
  - Certolizumab

Antibiotics

- Metronidazole: typical dose is 250 - 500mg po tid/qid, improvement seen after 6-8 weeks
  - Most studies are open label
  - Largest study conducted by Bernstein et al\(^1\)
    - 21 patients studied, healing seen in 83%
    - Three other studies found healing rate of 34 - 50%\(^2-5\)
- Fistulas re-occur once medicine is stopped
- Adverse events include metallic taste, glossitis, nausea and a distal peripheral sensory neuropathy

Antibiotics – Fistula Response

Fistula Response at 10 weeks

- Cipro: N=10, 40% response
- Metronidazole: N=7, 14% response
- Placebo: N=8, 13% response

p=0.43


Azathioprine / 6MP

- Five controlled trials were summarized in a meta-analysis1
  - 22 / 41 (54%) of patients who received AZA / 6-MP responded vs. 6 / 29 (21%) who received placebo
  - Pooled odds ratio was 4.44 in favor of fistula healing

- No dedicated trials – post hoc subgroups

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


Tacrolimus (FK-506)

• Double blinded study
• n=48
• Randomized to receive 0.20 mg/kg/day for 10 weeks
• Primary endpoint: improvement defined as closure of ≥ 50% fistulas and maintenance of closure for ≥ 4 weeks

Only 10% had closure of all fistulas

p=0.004
Infliximab for Crohn’s Perianal Fistulas

- Initial fistula response to infliximab
- n=94
- Primary endpoint: >50% reduction in open fistulas

Accent II: Infliximab for Maintaining Fistula Closure

- Percent of patients maintaining complete fistula closure
- n=306
- 54 weeks
- Primary endpoint: >50% reduction in open fistulas p=0.0009
Adalimumab: Complete Healing of Draining Fistulas

- Weeks 26 and 56: Randomized responders in CHARM trial
- n=70

Proportion of Fistula Responders with Fistula Closure

- Week 26 on Certolizumab Pegol PRECISE 2 subgroup


Proportion of Fistula Responders with Fistula Closure

- Week 26 on Certolizumab Pegol
- PRECISE 2 subgroup


Anti-TNF Agents: Adverse Events

- Immunogenicity
- Infection
  - Granulomatous (TB, histo, Listeria)
  - Viral, fungal
- Autoimmunity
- Lymphoproliferative dx?
- Neoplasm
  - Skin
  - Pediatric tumors
- Psoriaform 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

Approach to the Crohn’s Disease Patient with a Perianal Fistula

1. History and physical exam
2. Endoscopy to assess activity of Crohn’s disease
3. Imaging study (EUS or MRI) to delineate perianal disease process
4. Exam under anesthesia (EUA)

Simple Fistula Without Rectal Inflammation
- Antibiotics and AZA/6-MP
- Consider anti-TNF

Treatment Failure
1. Fistulotomy
2. Consider fibrin glue, fistula plug or endorectal advancement flap
3. If 1 or 2 fails, treat as complex fistulizing process

Treatment Success
- Continue maintenance AZA/6-MP and Anti-TNF (if started)

Simple Fistula With Rectal Inflammation
- Antibiotics, AZA/6-MP and Anti-TNF
  (Consider monitoring healing with repeat imaging study)

Treatment Failure
- Treat as complex fistulizing process
- Continue maintenance AZA/6-MP & Anti-TNF

Treatment Success
- Continue maintenance AZA/6-MP & Anti-TNF

Complex Fistula
1. Seton placement
2. Antibiotics, AZA/6-MP and Anti-TNF
   (Consider monitoring healing with repeat imaging study)

Treatment Failure
1. Remove seton
2. Continue maintenance AZA/6-MP and Anti-TNF

Treatment Success
- Consider Tacrolimus in selected pts
- Proctectomy

Nancy: Follow-Up

- Patient underwent rectal EUS which confirmed trans-sphincteric fistula with associated abscess (complex fistula)
- Received appropriate vaccinations
- Underwent EUA with seton placement and started azathioprine, 2.5 mg/kg/day (TPMT nl) and an anti-TNF
- Setons removed 4 months later once rectal EUS demonstrated an inactive fistula
- Continued maintenance azathioprine and anti-TNF