Immunomodulators and Complications of Surgery for Inflammatory Bowel Disease

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Disclosure of Affiliations
None

Medicines and Surgery for IBD

Cases: Sweet and Not So Sweet
• Blame the drugs when things go wrong?

History
Inflammatory cytokines
Effect of anti-TNFs on treatment philosophy
Effect of anti-TNFs on surgical complications

The Way We Hope It Goes
Not So Sweet Case

Recurrent ileal Crohn’s with intra-abdominal abscess
  • On biologics, steroids for recent flare

One week prior at outside hospital:
  • Ileocolic resection, drainage of abscess, takedown of ileosigmoid fistula

Surgeon calls me Sat. night
  • Patient in shock
  • Requesting transfer

Medicines and Surgery for IBD

Cases: Sweet and Not So Sweet

History
  • The story of Crohn (‘s)
  • Surgery and Medicine for IBD
  • When to operate

Inflammatory cytokines
Effect of anti-TNFs on treatment philosophy
Effect of anti-TNFs on surgical complications
The story of Crohn

- **AA Berg** (Chief of Surgery, Mt. Sinai) recognizes the disease and instructs his protégés (Leon Ginzburg and Gordon D. Oppenheimer) to investigate his 14 cases.

- Ginzberg collects data on 12 patients.

- **Burrill B. Crohn** (G1) collects data on 2 patients, appropriates Ginzburg’s data, presents series to AMA.

- Ginzburg and Oppenheimer present data from a larger series of patients to the American Gastroenterological Association 2 weeks later.

The story of Crohn

- Ginzburg brings charges against Crohn to Mt Sinai medical board and wins case.

- Ginzburg’s only victory is having his name appear on the paper, in which authors are listed in alphabetical order.

- Berg declines to have his name on manuscript because it has been his tradition that he only publish manuscripts with his name alone.

The story of Crohn

- **AA Berg** ultimately publishes his series.

  AA Berg.
  *An operative procedure for right-sided ulcerative colitis.*
The story of Crohn

- Crohn: gastroenterologist in NY
- Ginzburg: chief of surgery, Beth Israel Medical Center, NY
- Oppenheimer: chief of urology, Mt. Sinai

History of IBD Treatment

Surgery

- Mainstay of therapy for decades
  - Ileal Crohn’s
    - 1st stage: Ileocolic bypass
    - 2nd stage: Ileocolic resection
  - Ulcerative colitis
    - Ileostomy and cecostomy

Medical Treatment

- Steroids
  - Local or systemic
- 5-ASA compounds
  - Sulfasalazine (Azulfidine), Olsalazine (Asacol), Mesalamine (Asacol, Pentasa, Rowasa)
- Antibiotics
  - Metronidazole (Flagyl)
- Immunosuppressives
  - 6-Mercaptopyrimine (6-MP), Immuran
- Cytokine antagonists
  - Anti-TNF Ab, rh-IL-10, ICAM-1 antisense oligonucleotide (ISIS 2302), rhIL-11
- GMCSF

New Surgical Philosophy: IBD

When to operate

- Obstruction
- Perforation
- Bleeding
- Failure of medical therapy
- Prevention/treatment of colorectal cancer

Surgery as a last resort
New Surgical Philosophy: Crohn’s

**Inflammatory component**
- Medical management
- Operate when medical management fails to control symptoms

**Fibrotic component**
- If symptomatic, operate

Medicines and Surgery for IBD

Cases: Sweet and Not So Sweet History
- The story of Crohn’s
- Surgery and Medicine for IBD
- When to operate

**Inflammatory cytokines**
Effect of anti-TNFs on treatment philosophy
Effect of anti-TNFs on surgical complications
**History of IBD Treatment**

**Medical Treatment**
- **Steroids**
  - Local or systemic
- **5-ASA compounds**
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- **Antibiotics**
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  - 6-Mercaptopurine (6-MP), Immuran
- **Cytokine antagonists**
  - Anti-TNF-Ab, ch-IL-1, hIL-10, CAM-1 antisense oligonucleotide (ISIS 2302), rhIL-11
- **GMCSF**

**Anti-TNF agents**

- **Infliximab** (Remicade)
- **Adalimumab** (Humira)
- **Certolizumab** (Cimzia)
Sepsis Research

Initial insult in Inflammatory Bowel Disease

Infliximab for fistulizing Crohn’s

“Reduction” in fistula activity > 50%
- Infliximab 5mg/kg 68%
- Placebo 26%

“Temporary” closure of fistula
- Infliximab 5mg/kg 55%
- Placebo 13%
- Median duration until fistula reappeared: 3 months

Perianal Crohn’s Disease

Perianal Disease--”Watering Can Perineum”

Untreated Fistulous Disease
- 33 yo F refused medical care
  - Bacon poultice

Infliximab for fistulizing Crohn’s

Infliximab 5mg/kg + maintenance infliximab 36%
Infliximab 5mg/kg + no maintenance 19%


Perineal Crohn’s Disease

Medicines and Surgery for IBD

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History
- The story of Crohn (‘s)
- Surgery and Medicine for IBD
- When to operate
Inflammatory cytokines
Effect of anti-TNFs on treatment philosophy
- Too much medication?
Effect of anti-TNFs on surgical complications
Putting it all together
Management of IBD

The Past
- Steroids
- 5-ASA
- Surgery

The Present
- Steroids
  - Local or systemic
- 5-ASA compounds
- Sulfasalazine (Azulfidine), Olsalazine (Asacol), Mesalamine (Asacol, Pentasa, Rowasa)
- Metronidazole (Flagyl)
- 6-Mercaptopurine (6-MP), Immuran
- Cytokine antagonists
  - Anti-TNF Ab (Infliximab), rh-IL-10, ICAM-1 antisense oligonucleotide (ISIS 2302), rhIL-11
  - GMCSF
- Others
- Surgery

Too Much Medication?

“Do not let your patient lose their colon until you have tried all the medications.”
Daniel Present, MD
UCSF IBD conference
Nov. 6, 2004

Ileal Crohn’s

27 year old man: Ileal fistula through sigmoid mesocolon into left psoas to left flank and left groin
Ileal Crohn’s

Treated with 5-ASA, steroids, 6-MP, infliximab for 18 months
- Chronic septic state
- Weight loss, lethargy
- Forced to quit work
- Persistent pus drainage from left flank and left groin

Ileal Crohn’s: Too Much Medication

Ileal-psoas-cutaneous fistulas
- Treatment
  - Drain abscesses
  - Control fistulas
  - TPN
  - Antibiotics

Ileal Crohn’s: Too much medication?

OR
- Severe ileal disease with fistula through sigmoid mesocolon into left psoas and into left flank and groin
- Colon intrinsically normal
- Ileocolic resection, takedown of fistula, primary anastomosis
- Sigmoid colon spared

Ileal Crohn’s with fistula

Follow up at 6 months
- Patient happy
  - Doing well
  - Energy improved
  - No sepsis
  - Back to work
- Fistulas healed
- Off steroids
- Maintenance 5-ASA only

Wife unhappy
- Husband has “too much energy”
**Too Much Medication?**

**Mathematics**

**Gastroenterology**
- Medical “saves”
- Total n

*Failures are the problem of the surgeon*

**Surgery**
- Medical “failures”
- Total

*We rarely see the successes of medical therapy*

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**Social Problems in the Sandbox of Life**

**Bad terminology**
- It is not a “failure” for an IBD patient to require surgery
- It is better to operate prior to debilitation and malnutrition, than to force the patient to try every new drug available

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**Perioperative Complications**

**Associated with**
- Steroids
- Immunosuppressives
  - 6-MP, Imuran
- ?anti-TNF agents?

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**Medicines and Surgery for IBD**

**Cases: Sweet and Not So Sweet**

**History**

**Inflammatory cytokines**

**Effect of anti-TNFs on treatment philosophy**

**Effect of anti-TNFs on surgical complications**
- Single center data
- Meta-analysis

**Putting it all together**
Single center data: Toronto

**Preoperative biological therapy and short-term outcomes of abdominal surgery in patients with inflammatory bowel disease**

Matti Waterman,1,2 Wei Xu,3,4 Amreen Dinani,1,2 A Hillary Steinhart,1,3,4
Kathleen Croitoru,1,2 Geoffrey C Nguyen,1,2 Robin S McLeod,1,2
Gordon R Greenberg,1,2,4 Zone Cohen,1,4,5 Mark S Silverberg1,2,4

*Gut.* 2013. 62: 387-394

Complications

No difference in outcomes

**Time Interval from Last Dose**

No difference in outcomes

**Readmissions**

Cedar-Sinai, LA
Readmissions

Increase as number of medications increase

Meta-analysis: Complications

Anti-tumor Necrosis Factor and Postoperative Complications in Crohn’s Disease: Systematic Review and Meta-analysis

Total Complications

Increased with anti-TNFs

Complications: Meta-analysis

Met-analysis: peri-operative anti-TNF treatment and post-operative complications in patients with inflammatory bowel disease

N. Nanda, D. Charlton & J. K. Marshall
Infectious Complications

Increase with anti-TNFs

Non-Infectious Complications

Increase with anti-TNFs

Total Complications

Increase with anti-TNFs

Problems with the Data
Problems with the Data

No prospective, randomized trials
Selection bias
  • Inherent in study design

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Putting it all together
  • Perioperative management philosophy
  • Stop the meds preop?
  • Top down treatment algorithm?

Crohn’s Disease: Surgical Philosophy

Principles of management
  • Attempt to convert every “urgent” situation into an elective operation

Crohn’s

Principles of Management
  • Control sepsis
    • Percutaneous drainage of abscesses
    • Antibiotics
  • Bowel rest/Improve nutrition
    • TPN
  • Intestinal evaluation
  • Resection of disease
    • May be amenable to laparoscopic approach

A Case: She’s all blocked up

- TI disease since diagnosis
- Colonoscopy: normal colon
- Baseline meds: Certolizumab (Cimzia), 5-ASA, Entocort
- Several admissions for flares, managed with steroids
- Clinically obstructed
- Not septic
- Tender phlegmon in RLQ
- Obesity, Otherwise healthy

What is the next step?

A. Antibiotics
B. Prednisone
C. Infliximab (Remicade)
D. Ileocolic resection
The Big Answer

Don’t stop the meds

When are medications most effective?

Early on, when inflammation predomnates

Top down approach, medication

Biologics first

Top down approach, overall

Surgery first*

Biologics as maintenance
Top down, overall

* Only if we can select those patients who would have long symptom-free period or no disease recurrence

Inflammatory Bowel Disease

Management Strategy

- Team Approach
  - Gastroenterologist
  - Colon and rectal surgeon