Biologics for CD and CUC: The Impact on Surgical Outcomes

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Overview

• Antibody based medications (biologics) are highly effective in the treatment of Crohn’s disease (CD) and have shown some efficacy in the management of chronic ulcerative colitis (CUC).
• The impact on these agents on the short-term surgical outcomes is unclear. The conflicting reports most likely are related to the different nature of the diseases and operations performed.

Principles of Successful Intestinal Surgery

• Operate on a patient when they are “healthy”
  • Maximize nutrition status
  • Requiring no blood transfusions
  • Control any local sepsis
  • No secondary infections
• Disease activity controlled to minimize systemic inflammatory response
• Remember wound healing is an immune based process

All impact immune status

Risk Factors for Anastomotic Complications

• Patient
  • Obesity
  • Diabetes
  • Immuno-suppression
  • Smoking
  • Malnutrition
  • Infection
  • Anemia
  • Requiring blood transfusion
  • Cardiopulmonary disease
• Technical
  • Inflammation/infection
  • Tension
  • Location
    • Small bowel low risk
    • Colon moderate risk
    • Rectal highest risk
  • Poor blood supply
  • Size differences
**Types of Surgery**

- **Crohn’s Disease**
  - Predominately small bowel surgery
  - Small bowel to colon or upper rectum
  - Infrequently colon-colon
  - “Never” mid to low rectal surgery

- **Ulcerative Colitis**
  - Total proctocolectomy (TPC) with end ileostomy
  - TPC with ileal-pouch anal anastomosis (IPAA)
  - Small bowel to ultra-low rectum or anal canal tissue

- **Crohn’s Disease**
  - Operating for symptoms after maximal medical therapy
    - Obstruction
    - Fistulas
    - Intractable poor GI function
    - Sepsis resolved or controlled
  - Delay intervention until patient’s overall health is maximized and nutrition optimized

**Crohn’s Disease**

- The goal in CD is to resect all grossly involved intestine and anastomose normal healthy bowel together.

**Impact of Biologic Therapy on Complex Fistulizing CD**

- Abdominal enterocutaneous fistula
  - Anecdotal experience
- Perianal (including vaginal fistulas)
  - Induction therapy (12 weeks)
    - 46% complete clinical response
    - 68% partial improvement
  - Sands, et al. NEJM 2004;350:876
  - Long-term results without maintenance
    - 90% recurrence at 1 year
  - Long-term biologic therapy does not seem to impact complete healing nor impact the success of surgical approaches
    - Gaertner, et al. DCR 2007;50:1754
Impact of Pre-operative Biologic Therapy on Abdominal CD Surgery Outcomes

- Mayo Clinic experience
  - 270 patients (52 IFX treatment); different surgeries
  - Most were on multiple agents including steroids
  - No difference in 30-day complications

- Cleveland Clinic experience
  - 389 primary ileocolic resections (60 IFX treatment within 3 months)
  - Immunomodulator use higher in IFX, steroids higher in non-IFX
  - Higher post-op septic complications in IFX group
  - Proximal diversion decreased risk in IFX group

Ulcerative Colitis

- Operating for unremitting disease activity
  - Hospitalized patients
    - Bleeding and significant protein loss
  - Recent weight loss
  - Multiple medications often with steroids
  - Outpatients
    - Would have been in-patients 7-10 years ago
    - Persistent symptoms
      - Weight loss/poor nutritional status
      - Anemic
      - Chronically ill
      - Multiple immunosuppressives often with recent steroids

- Restorative surgery (IPAA)
  - Anastomosing in the ultra-low rectum
  - Anastomosis under some tension
  - Blood supply tenuous
  - Half of the anastomosis has inflamed, poor quality tissue

Long-term IPAA Success

- Number one predictor of poor pouch function and pouch failure is a postoperative pelvic/abdominal abscess or pelvic sepsis
Retrospective study (2002-2005)
- Mayo Clinic, Rochester
- 301 patients (47 IFX, 254 no-IFX preop)
- Only UC patients (no CD)
- All underwent TPC with IPAA and DI
- 30 day morbidity and mortality

Results

• IFX patients coming to IPAA were sicker
  • Worse disease severity
  • Multiple agents (AZA, steroids)
• Adjusting for these variables, including low, moderate, and high dose steroids, only preoperative use of IFX was associated with increased infectious complication
• Study unable to establish any causation more likely a surrogate for a higher risk surgical patient

Other Views and Concerns

• Mor et al. Diseases of Colon Rectum 2008
  • Two-stage IPAA patients (2000-2006)
  • Cleveland Clinic
  • Case-matched retrospective series (46 patients with IFX preop)
    • Random match based on age, sex, date of operation, indication
    • IFX patients
      • Early complications 3.54 times control
      • Sepsis rate 13.8 times control
• Concerns: small number of events, long time span, long observation period for complications, confounders in patient selection
Other Views and Concerns

- Schlueder et. DCR 2007
  - 17 patients (IFX) compared to 134 (no IFX)
  - Cedars Sinai Medical Center
  - No influence of IFX on total complications
  - Interestingly, increased complication rate in patients on preop IFX + CyA
  - Concerns: small number of IPAA w/ IFX (n=5), included subtotal colectomy patients, defined complications as major/ minor

- Ferrante et al. IBD 2009
  - 141 UC patients (10 year)
  - University Hospital Leuven, Belgium
  - 22 received IFX (9 IPAA; 7 w/ , 2 w/o DI)
  - No association with post-op infection and IFX
  - Steroids and one-stage IPAA associated with infectious complications
  - Concerns: long time period, small numbers, heterogeneous surgical population, multi-staged, significant surgical selection bias (9% no DI in IFX; 34% in control, higher TPC-BI 59% to 24% in the IFX group)

- Kunitake et al. J Gastrointest Surg 2008
  - Massachusetts General Hospital
  - 413 patients (CD 45.5%; UC 37.8%, IC 16.5%) over 14 years
  - No association with IFX and complications
  - Concerns
    - Very long period of observation (14 years!)
    - Mixing disease processes (CD, UC, IC)
    - UC group:
      - heterogeneous surgical procedures including unusual UC cases
      - no separate IPAA analysis
      - Separate classifications of infectious and leak complications and separate analysis

- Pre-operative infliximab exposure and the occurrence of post-operative complications following proctocolectomy and ileal pouch-anal anastomosis (IPAA) for ulcerative colitis (UC).
  - Swoger and Loftus et al. DDW 2009
  - 436 IPAA UC patients, 2002-2007, Mayo Clinic, Rochester
  - 25% preoperative IFX exposure (n=109)
  - 43% immunomodulators, 64% steroids
  - Univariate analysis no relationship with infectious complications
  - Multivariate analysis only IFX treatment (of medications) was associated with post-op early infectious complications, not steroid use; increased BMI and fulminant disease were also associated
**Is IFX Resulting in Increased Infectious Problems in UC?**

- **No**
- **Is there an influence wound healing problems? Possibly.**
  - An abscess/infection is the result of a leak from a failure of appropriate wound healing (anastomosis, incisions)

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**Parallel Data**

**Rates of Serious Infection, Including Site-Specific and Bacterial Intracellular Infection, in Rheumatoid Arthritis Patients Receiving Anti-Tumor Necrosis Factor Therapy**

Results from the British Society for Rheumatology Biologics Register

- **Registry database**
  - 7,644 anti-TNF treatment, 1,354 other immunomodulator/steroid therapy
  - No association with overall infectious complications (opportunistic infections, pneumonia, urinary tract)
  - Significantly increased risk of skin and soft tissue infections in anti-TNF treated patients

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**Parallel Data**

Analysis of the tensile strength on the healing of the abdominal wall of rats treated with infliximab

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**Parallel Data**

**Tumor Necrosis Factor Inhibitor Therapy and Risk of Serious Postoperative Orthopedic Infection in Rheumatoid Arthritis**

Small retrospective analysis of RA patients (n=91) undergoing joint surgery at Johns Hopkins

- Uni- and multivariate only anti-TNF treatment was associated with post-op joint/soft tissue infection
Summary

• Biologic therapies are an important component of IBD therapy
• Powerful immuno-suppressive or a combination of agents that may impair wound healing may result in increased post-operative septic complications
• CD patients often come to surgery with less active disease and require different types of procedures compared to CUC patients
• Patients are coming to surgery with longer duration of disease activity, more intense immune suppression
• More conservative operations (ie proximal diversions) or staged operations might be the appropriate approach to the contemporary IBD patient.

Thank You
Questions?