Management of Postoperative Crohn’s Disease: A New Approach to an Old Problem

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Despite IBD medications…………

………………...60%-75% of Crohn’s disease patients require intestinal resection at some point in their lifetime,

and.........surgery is not a cure....
Background

- Histologic recurrence occurs as early as one week after surgery\(^1\)
- Endoscopic Recurrence: 70-90% one year after resection\(^2,3\)
- Clinical Recurrence: 30% by 3 years and 60% by 10 years\(^4\)

What is the best way to identify post-operative recurrence?

• Clinical?
• Colonoscopy?
• Radiology?
• ESR/CRP?
• Other?
Predictability of the postoperative course of Crohn's disease.


Gastroenterology. 1990;99:956-963
Endoscopic Recurrence Score

- **i0**: no lesions
- **i1**: \( \leq 5 \) aphthous lesions
- **i2**: > 5 aphthous lesions with normal intervening mucosa
- **i3**: diffuse aphthous ileitis with diffusely inflamed mucosa
- **i4**: diffuse inflammation with large ulcers, nodules, and/or narrowing

• i0 or i1 low risk of endoscopic progression: clinical recurrence rates <10% at 10 yrs

• i2 clinical recurrence rate 20% at 5 years

• i3 or i4 clinical recurrence rates of 50-100% over 5 years with high likelihood of re-operation

Risk Factors Associated with Postoperative CD Recurrence

- Active cigarette smoking
- Penetrating (fistulizing) disease
- Ileocolonic disease
- History of prior resection
What to do after surgery?

• 27 yo male ileal resection for intra-abd abscess: diagnosis of CD made at surgery

• 62 yo female with 22 years of CD and no prior Rx: resection of 5 cm TI stricture.

• 35 yo female smoker and 15 cm TI inflammatory stenosis resected for pSBO.
Algorithm for post-op CD management

More Questions than Answers

- 5-ASA?
- Antibiotics?
- Steroids?
- 6MP/AZA?

What about anti-TNFs/Biologics?

- How should we follow these patients?
- When to Colonosocope?
- Are there predictors of disease recurrence?
RCTs for Prevention of Postoperative CD Recurrence

- 5-aminosalicylates (including sulfasalazine)
- Budesonide
- Nitroimidazole antibiotics
- 6 meraptopurine (MP) and azathioprine (AZA)
Randomized Controlled Post-Operative Trials: One Year Recurrence Rates

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At best, endoscopic recurrence rates with standard meds are 45%

This means that despite postop meds, nearly half of CD pts who have undergone a resection will ultimately have clinical recurrence and likely require future surgery.
Is there a better way to prevent post-op Crohn’s disease recurrence?
Infliximab Prevents Crohn’s Disease Recurrence after Ileal Resection

Study Design

- Randomized, two-armed, double-blind, placebo-controlled trial

- Sample size power calculation
  - Assuming 80.0% recurrence in placebo group, 20.7% recurrence in infliximab group
  - 24 total pts needed (2-sided type I error rate of 0.05)

- 24 patients randomly assigned to **infliximab 5mg/kg** or **placebo** within 4 weeks of surgery (0, 2, 6, and every 8 weeks for one year)
Primary outcome:
Proportion of patients with endoscopic recurrence one year after ileal resection for Crohn’s disease

Secondary outcomes:
– Clinical recurrence (CDAI > 200)
– Clinical remission (CDAI < 150)
– Histological recurrence
Endoscopic Recurrence Score

Endoscopic Remission

• i0: no lesions
• i1: ≤ 5 aphthous lesions

Endoscopic Recurrence

• i2: > 5 aphthous lesions with normal intervening mucosa
• i3: diffuse aphthous ileitis with diffusely inflamed mucosa
• i4: diffuse inflammation with large ulcers, nodules, and/or narrowing

**Results**

Patients Screened  
\[ n=31 \]

Patients Eligible  
\[ n=24 \]

Randomization*  
- **Infliximab**  
  \[ n=11 \]
- **Placebo**  
  \[ n=13 \]

End of study endoscopy  
Intent to treat analysis

* Random assignment in a blocked manner with small sample size did not insure exact 1:1 treatment allocation
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Endoscopic Recurrence Reduced in Infliximab Treated Patients

Endoscopic Recurrence defined as endoscopic scores of i2, i3, or i4.
Infliximab (n=11)  
Placebo (n=13)  

Endoscopic grade 1 year after surgery
Histological recurrence defined by neutrophil infiltration in lamina propria and epithelium.

- **Infliximab (n=11)**: 3/11 (27.3%)
- **Placebo (n=13)**: 11/13 (84.6%)

**Histologic Recurrence Reduced in Infliximab Treated Patients**

Infliximab vs placebo, p=0.01
One Year Clinical Recurrence Reduced in Infliximab Treated Patients

Clinical recurrence defined by 54 week CDAI > 200.

Infliximab vs placebo
p=0.046

Clinical Recurrence

% patients

0 5 10 15 20 25 30 35 40 45

Infliximab (n=11) Placebo (n=13)
Conclusions

- Infliximab is effective at preventing one year endoscopic, clinical, and histological postoperative recurrence of Crohn’s disease.

- There were no adverse events related to the administration of infliximab in the immediate postoperative period.
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Post-Op RCTs: Most recurrence rates are based on one year results.
Risk of Post-Op Recurrence

- **Very Low**
  - No Meds
  - Colonoscopy 6-12 months post-op
    - No Recurrence
      - Colonoscopy every 1-3 yrs
    - Recurrence
      - Immunomodulator or anti-TNF

- **Low/Mod.**
  - 6MP or AZA ± metronidazole
  - Colonoscopy 6-12 months post-op
    - No Recurrence
    - Recurrence
      - Colonoscopy every 1-3 yrs
      - ↑ anti-TNF or Δ biologics

- **High**
  - Anti-TNF
  - Colonoscopy 6-12 months post-op
    - No Recurrence
    - Recurrence

**Penetrating disease, ≥ 2 surgeries**
What to do after surgery?

- 27 yo male ileal resection for intra-abd abscess: diagnosis of CD made at surgery: **Infliximab and rescope at 1 year**

- 62 yo female with 22 years of CD and no prior Rx: resection of 5 cm TI stricture: **No meds and rescope 6-12 months**

- 35 yo female smoker and 15 cm TI inflammatory stenosis resected for pSBO: **Favor anti-TNF but other option - AZA/6MP ± metronidazole with colonoscopy 6 months.**
Future direction

• Post-op CD provides a unique model for natural course of disease study
  – Extrapolate to undiagnosed or newly dx’d
  – Potential to evaluate true top-down Rx
• Treatment initiated in response to endoscopic recurrence vs. prophylaxis?
• Are all biologics equally efficacious at preventing postop CD?
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