Prevention and Management of Postoperative Crohn’s disease

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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
- Endoscopic Recurrence: 70-90% one year after resection
- Clinical Recurrence: 30% by 3 years and 60% by 10 years


Predictability of the postoperative course of Crohn's disease.

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

- **i0**: no lesions
- **i1**: ≤ 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


Rutgeerts Endoscopic Scoring System
Neoterminal Ileum
**Endoscopic Recurrence correlates with Clinical Recurrence (one year)**

- 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

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**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

<table>
<thead>
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<th>Clinical Recurrence</th>
<th>Endoscopic recurrence</th>
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<td>Placebo</td>
<td>25% – 77%</td>
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Regueiro M. Inflammatory Bowel Diseases. 2009 (in press)

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

Regueiro M, Schraut W, Baidoo L, Kip KE, Sepulveda AR, Pesci M, Harrison J, Plevy SE.

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)

Study Outcomes

• **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**
- \(i_0\): no lesions
- \(i_1\): \(\leq 5\) aphthous lesions

**Endoscopic Recurrence**
- \(i_2\): > 5 aphthous lesions with normal intervening mucosa
- \(i_3\): diffuse aphthous ileitis with diffusely inflamed mucosa
- \(i_4\): diffuse inflammation with large ulcers, nodules, and/or narrowing


Endoscopic Recurrence Reduced in Infliximab Treated Patients

Endoscopic Recurrence defined as endoscopic scores of \(i_2\), \(i_3\), or \(i_4\).
Infliximab (n=11)
Placebo (n=13)

Endoscopic grade 1 year after surgery

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
### Clinical Recurrence vs. Endoscopic Recurrence

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Regueiro M. *Inflammatory Bowel Diseases*. 2009 (in press)

### Risk Factors Associated with Postoperative CD Recurrence

- Active cigarette smoking
- Early age of surgery (<30)
- Short time to first surgery
- Ileocolonic disease
- Penetrating (fistulizing) disease
- History of prior resection
Risk of Post-Op Recurrence

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

Moderate
- 6MP or AZA ± metronidazole
  - Colonoscopy 6-12 months post-op
    - No Recurrence
    - Recurrence
      - Colonoscopy every 1-3 yrs

High
- Anti-TNF
  - Colonoscopy 6-12 months post-op
    - No Recurrence
    - Recurrence
      - Colonoscopy every 1-3 yrs
      - anti-TNF or Δ biologics

Penetrating disease, > 2 surgeries

3 year follow up from Infliximab post-op study

Regueiro M, et al. ACG 2009
Primary aim: To examine long-term endoscopic CD remission and recurrence rates after surgery in the postop prevention trial.

Among the 24 pts, a total of 48 post-surgical endoscopic evaluations have been performed to date.

Patients Initially Randomized to Infliximab
(one year postop – end of RCT)
Patients Initially Randomized to Infliximab
(~3 years postop)

Patients Initially Randomized to Placebo
(one year postop- end of RCT)
Conclusions from 3 yr f/u

- Pts who continue infliximab maintain remission
- Pts who stop infliximab are more likely to have recurrent ds
- Most placebo pts who had an endoscopic recurrence 1 yr after surgery had a response to open label infliximab.
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 with induction of *very deep remission*
• Treatment initiated in response to endoscopic recurrence vs. prophylaxis?
• Are all biologics equally efficacious at preventing postop CD?

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