Preventing Postoperative Recurrence in Crohn's Disease

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Medical Management of Postop Crohn's Disease: Early Treatment Versus Watchful Waiting
50-65% of CD pts still go to surgery despite earlier and more IMM/antiTNF usage

IN 2016:
CD treatment relies on initiation of med rx in response to ds – in many, the tissue damage may be irreversible...therefore...

The Natural Course of postop CD

Recurrence is clinically silent initially

Histologic Endoscopic Radiologic Clinical Surgical

Within 1 week 70-90% by 1 yr Tissue damage 30% 3 yr 60% 5 yr 50% by 5 yrs

**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


>70% of Pts Have i2,3,4 Recurrence 1 Year after Surgery – Rutgeerts et al Gastro 1990

- **i0** and **i1** remission
  - low likelihood of progression

- **i2**, **i3**, **i4** recurrence
  - Likely progression to another surgery
Algorithm for post-op CD management

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

What about anti-TNFs/Biologics?
How should we follow these patients?
When to Colonoscopy?
Are there predictors of disease recurrence?

More Questions than Answers

Case 1

- 32-year-old male, smoker with Crohn’s disease for 5 years.
- Only prior treatment 5ASAs and 1-2x/year steroids.
- Now with a small bowel obstruction.
Case 1 Postop management

• An ileocolonic resection is performed – 10 cm of TI with a stricture and active Crohn’s as well as the cecum were removed
• Now what?
Case 1 - Conclusion

• 32-year-old male, smoker with Crohn’s disease for 5 years.
• Only prior treatment 5ASAs and 1-2x/year steroids.
• Now with a small bowel obstruction.
• An ileocolonic resection is performed – 10cm of TI with a stricture and active Crohn’s as well as the cecum were removed
• Quit smoking, AZA, scope 6 months

Case 2

• 43-year-old female with newly dx’d Crohn’s ileitis develops severe abd pain and fever
• She has not been on meds as the dx is new
• She is a smoker, no NSAIDs, no FHx IBD
• A CT scan is performed
Case 2

- After the abscess is drained and she is given abx, surgery is performed
- She has an ileocecal resection and primary anastomosis—ileal-ileal fistula with an associated abscess
- No other disease, now what?
Case 2

- 43-year-old female with newly dx’d Crohn’s ileitis develops severe abd pain and fever
- She has not been on meds as the dx is new
- She is a smoker, no NSAIDs, no FHx IBD
- A CT scan is performed: abscess is drained and ileocecal resection
- Quit smoking, antiTNF/IMM, scope 6-12 months

Case 3

- A 67-year-old male with a 40 year history of CD presents with an small bowel obstruction.
- He has only received mesalamine and one course of steroids at diagnosis.
- He has had 3 colonoscopies over the past 15 years and each revealed a 5 cm stricture but minimal Crohn’s ds activity
Small bowel follow through

Case 3 – postop

• The surgeon finds a very short, fibrotic stricture without active Crohn’s
• Now what?
Case 3

• A 67-year-old male with a 40 year history of CD presents with an small bowel obstruction.
• He has only received mesalamine and one course of steroids at diagnosis.
• He has had 3 colonoscopes over the past 15 years and each revealed a 5 cm stricture but minimal Crohn’s ds activity
• Stricture is resected and no other ds
• No meds and scope at 6 mos.

Case 4

• 33-year-old female presents with severe abd pain and fever
• She is a smoker, no NSAIDs, no FHx IBD
• A CT scan is performed
Case 4

- The abscess is drained and she is given abx, she feels better and fevers resolve
- She wants to avoid surgery
- She quits smoking
Case 4 (cont.)

- She is placed on infliximab and azathioprine
- Over the next 6 mos. she’s in and out of the hospital with pain and fevers
- Her CT scan shows no improvement
- Ileocecal resection and primary anastomosis– ileal-ileal fistula and an abscess, no other ds
- Now what? Postop: do you continue IFX/AZA or stop or do something else?
Case 4

- 33-year-old female presents with severe abd pain and fever
- She is a smoker, no NSAIDs, no FHx IBD
- A CT scan is performed – abscess drained, placed on IFX/AZA, fails and goes to surgery 6 mos later (fistula)
- Continue IFX/AZA postop and scope 6 mos.

Case 5

- A 45-year-old man with severe Crohn’s colitis and perianal fistula has a colectomy and ileostomy (surgeon finds no ileal ds).
- He has previously received thiopurines, two different antiTNFs, steroids, abx and nothing seemed to work.
Do Crohn’s ds patients who have a colectomy and end ileostomy need rx?

Case 5 – postop management ileoostomy

• He sees you 4 weeks after surgery. He is doing extremely well with the ileostomy and asks you about meds and whether he needs an ileoscopy at some point.
• What do you do now?
Case 5

• A 45-year-old man with severe Crohn’s colitis and perianal fistula has a colectomy and ileostomy (surgeon finds no ileal ds).
• He has previously received thiopurines, two different antiTNFs, steroids, abx and nothing seemed to work.
• Without prior ileal ds, low likelihood of CD recurrence, no postop meds and ileoscopy 1 yr later

Early Treatment:
Medications for Preventing Postoperative Crohn’s Disease
### Summary of Postop RCTs

<table>
<thead>
<tr>
<th>Postop Prevention RCTs</th>
<th>Clinical Recurrence</th>
<th>Endoscopic recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>25-77%</td>
<td>53-79%</td>
</tr>
<tr>
<td>5 ASA</td>
<td>24-58%</td>
<td>63-66%</td>
</tr>
<tr>
<td>Budesonide</td>
<td>19-32%</td>
<td>52-57%</td>
</tr>
<tr>
<td>Nitroimidazole</td>
<td>7-8%</td>
<td>52-54%</td>
</tr>
<tr>
<td>AZA/6MP</td>
<td>34-50%</td>
<td>42-44%</td>
</tr>
</tbody>
</table>

Regueiro M. *Inflammatory Bowel Diseases*. 2009

### Endoscopic Recurrence Reduced in Infliximab Treated Patients

- **Infliximab (n=11)**
  - Endoscopic Recurrence: 1/11
- **Placebo (n=13)**
  - Endoscopic Recurrence: 11/13

Infliximab vs placebo: p=0.0006

Endoscopic Recurrence defined as endoscopic scores of i2, i3, or i4.
### PO- Endo Recur

<table>
<thead>
<tr>
<th>Study</th>
<th>antiTNF</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sorrentino¹ (MTX/IFX v 5ASA 2yr)</td>
<td>0%</td>
<td>100% (5ASA)</td>
</tr>
<tr>
<td>Regueiro² (IFX vs PBO RCT 1 yr)</td>
<td>9%</td>
<td>85% (PBO)</td>
</tr>
<tr>
<td>Yoshida³ (IFX vs PBO Open 1 yr)</td>
<td>21%</td>
<td>81% (5ASA)</td>
</tr>
<tr>
<td>Armuzzi⁸ (IFX vs AZA Open 1 yr)</td>
<td>9%</td>
<td>40% (AZA)</td>
</tr>
<tr>
<td>Fernandez-Blanco⁴ (ADA)</td>
<td>10%</td>
<td>N/A</td>
</tr>
<tr>
<td>Papamichael⁵ (ADA 6m)</td>
<td>0%</td>
<td>N/A</td>
</tr>
<tr>
<td>Savarino⁶ (ADA 3yr)</td>
<td>0%</td>
<td>N/A</td>
</tr>
<tr>
<td>Aguas⁷ (ADA 1 yr)</td>
<td>21%</td>
<td>N/A</td>
</tr>
<tr>
<td>De Cruz⁹ (ADA vs AZA 6mos)</td>
<td>6%</td>
<td>38% (AZA)</td>
</tr>
<tr>
<td>Savarino¹⁰ (ADA vs AZA vs 5ASA 2 yrs)</td>
<td>6%</td>
<td>65% (AZA), 83%(5ASA)</td>
</tr>
</tbody>
</table>

## Infliximab for Prevention of Recurrence of Post-Surgical Crohn’s Disease Following Ileocolonic Resection: a Randomized, Placebo-Controlled Study (PREVENT)

M Regueiro¹, BG Feagan², B Zou³, J Johanns³, M Blank⁴, M Chevrier³, S Plevy³, J Popp³, F Cornillie⁵, M. Lukas⁶, S. Danese⁷, P Gionchetti⁸, M Molenda⁴, SB Hanauer⁹, W Reinisch⁴⁰, WJ Sandborn¹⁰, D Sorrentino¹², P Rutgeerts¹³

¹University of Pittsburgh Medical Center, ²Robarts Research Institute, University of Western Ontario, ³Janssen Research and Development, LLC, ⁴Janssen Scientific Affairs, LLC, ⁵MSD International, ⁶Charles University, ⁷Istituto Clinico Humanitas, ⁸DIMEC, S. Orsola-Malpighi Hospital, University of Bologna, ⁹Northwestern Feinberg School of Medicine, ¹⁰McMaster University, ¹¹University of California San Diego, ¹²Virginia Tech Carilion School of Medicine, ¹³Catholic University of Leuven

This study was supported by Janssen Scientific Affairs, LLC.
Subjects with Clinical Recurrence Prior to or at Week 76 and Week 104

**Primary Endpoint**

<table>
<thead>
<tr>
<th></th>
<th>Placebo (N=150)</th>
<th>Infliximab 5 mg/kg (N=147)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Recurrence Prior to or at Week 76</td>
<td>20.0%</td>
<td>12.9%</td>
</tr>
<tr>
<td>Clinical Recurrence prior to or at Week 104</td>
<td>25.3%</td>
<td>17.7%</td>
</tr>
</tbody>
</table>

P-values based on the Cochran-Mantel-Haenszel chi-square test stratified by the number of risk factors for recurrence of active CD (1 or >1) and baseline use (yes/no) of an immunosuppressive (i.e., AZA, 6-MP, or MTX).

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Secondary Endpoint: Subjects with Endoscopic Recurrence Prior to or at Week 76

<table>
<thead>
<tr>
<th></th>
<th>Placebo (N=150)</th>
<th>Infliximab 5 mg/kg (N=147)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endoscopic Recurrence Only Based on Endoscopic Criteria (i.e., Rutgeerts score ≥2)</td>
<td>51.3%</td>
<td>22.4%</td>
</tr>
<tr>
<td>Endoscopic Recurrence with Treatment Failure Rule and Other Data Handling Rules Applied</td>
<td>60.6%</td>
<td>30.6%</td>
</tr>
</tbody>
</table>

†Nominal p-values based on the Cochran-Mantel-Haenszel chi-square test stratified by the number of risk factors for recurrence of active CD (1 or >1) and baseline use (yes/no) of an immunosuppressive (i.e., AZA, 6-MP, or MTX).
ok, that was the early treatment approach, but what about......

Watchful Waiting and Treat Postoperative Crohn’s recurrence?

Crohn’s disease management after intestinal resection: a randomized (postoperative Crohn’s endoscopic recurrence POCER) trial

Study Design

- **Primary endpoint:** 18 month endoscopic recurrence in Crohn’s disease pts after bowel resection

- **Design:** After surgery pts randomized to:
  - (active care) 6 month colonoscopy with step-up rxent for endoscopic recurrence (≥i2)
  - (standard care) no 6 month colonoscopy

Treatment Stratified by Risk

- **All pts:** metronidazole 400mg bid x 3 mos. (if not tolerating, then 200mg bid or stop)

- **High risk for recurrence:** ≥1 factor smoking, perforating ds, previous resection
  - AZA 2mg/kg or 6MP 1.5mg/kg (if intolerant: Adalimumab 160/80/40qow)

- **Low risk for recurrence:** 0 risk factors
  - metronidazole and no other rxent
49% vs. 67% endoscopic recurrence at 18 months in active vs. standard care pts
By scoping at 6 mos and intensifying rx
18% lower rate of endoscopic recurrence

By scoping at 6 mos and intensifying rx
18% lower rate of endoscopic recurrence

6 month Endoscopic Recurrence in Thiopurine
and Adalimumab treated pts

*6 mos. rates only include active care group
Standard care group only had 18 mos. Colonoscopy
Study not designed to compare endoscopic recurrence between thiopurines and adalimumab
This means that “waiting” on antiTNF and giving thiopurine, nearly half of the pts had recurrence at 6 months

*6 mos. rates only include active care group
Standard care group only had 18 mos. Colonoscopy
Study not designed to compare endoscopic recurrence between thiopurines and adalimumab

2 Possible Approaches to Postop Crohn’s disease

1. **Watchful Waiting** for low risk pts, but treat high risk pts with IMM and/or antiTNF
2. **Treat All** but lowest risk immediately after surgery

- The main difference is how risk is defined ....
**Risk Factors Associated with Postoperative CD Recurrence**

- **Relative Risk Factors**
  - Early age of surgery (<30)
  - Short time to first surgery
  - Ileocolonic disease
- **Active cigarette smoking**
- **Progressed to surgery despite immunomodulators**
- **Penetrating (fistulizing) disease**
- **History of prior resection**

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**The Watchful Waiting Approach**

…based on POCER…..
My Approach – Almost All of my patients start a med after surgery

…but NOT necessarily an antiTNF
- take into account Risk Factors for Recurrence
Risk of Post-Op Recurrence Early Rx for ALL but Low Risk

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

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

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

1st s
Penetrating disease, > 2 surgeries
CD