PRACTICAL EDUCATION FOR THE ROAD AHEAD

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2020 Management of Post-operative CD: The Road Ahead

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The postoperative Crohn’s disease (CD) model may give us a “glimpse” into the natural course of immune-mediated diseases

- ...unlike rheumatologic and dermatologic diseases, we can remove the diseased segment in CD and “start over”
The Natural Course of Postop CD

Recurrence is clinically silent initially

Histologic
Within 1 week

Endoscopic
70-90% by 1 yr

Radiologic
Tissue damage

Clinical
30% 3 yr
60% 5 yr

Surgical
50% by 5 yrs

Endoscopic Recurrence Score

Low Risk for Postoperative Recurrence

- **i0**: no lesions
- **i1**: < 5 aphthous lesions

High Risk for Clinical and Surgical 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

Two Approaches to Postop Crohn’s Disease

1. Start treatment 2-4 weeks after surgery
2. Wait until endoscopic recurrence (perform colonoscopy 6 months from surgery)
Start treatment postop to prevent recurrence

..........but which treatment????????????

1) Microbiome altering (antibiotics)
2) Biologics

"..endoscopic recurrence is associated with strong changes in ileal mucosa-associated microbiota with a reduction in alpha diversity, an increase in several members of the Proteobacteria phylum and a decrease in several members of the Lachnospiraceae and the Ruminococcaceae families within the Firmicutes phylum."

“At the time of surgery, we identified several bacterial taxa associated with endoscopic recurrence and that can better predict relapse than usual clinical risk factors.”
Early Treatment: Nitroimidazole Antibiotics

• Original placebo controlled trials
  • Metronidazole$^1$
    • Metronidazole (20 mg/kg/day) vs. placebo for 3 months
  • Ornidazole$^2$
    • Ornidazole (500mg bid) vs. placebo for 1 year

Endoscopic recurrence at 1 year

80 patients, Ornidazole 1g/day started within 1 week of surgery

Limitation = Intolerance to med

Low-Dose Metronidazole is Associated With a Decreased Rate of Endoscopic Recurrence of Crohn’s Disease After Ileal Resection

- 250 mg three times per day for 3 months (retrospective cohort study)
- Primary outcome: endoscopic recurrence ($> i2$) within 12 months
- 23% adverse events and 8% stopped due to AEs
Early Treatment:
Anti-TNF for Preventing Postoperative Crohn’s Disease
RCT: Infliximab Prevents Crohn’s Disease Recurrence after Ileal Resection
Endoscopic Recurrence Reduced in Infliximab-Treated Patients

Endoscopic Recurrence defined as endoscopic scores of i2, i3, or i4.

Small Trials can inform Larger Studies

#24

The Postop Bus
<table>
<thead>
<tr>
<th>Study Description</th>
<th>Anti-TNF</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>
...and the large international postop trial...

The PREVENT Study
Primary Endpoint

Clinical Recurrence
Subjects with Clinical Recurrence Prior to or at Week 76 and Week 104

Primary Endpoint

- Clinical Recurrence Prior to or at Week 76
  - Placebo (N=150): 20.0%
  - Infliximab 5 mg/kg (N=147): 12.9%
  - P-value: 0.097

- Clinical Recurrence prior to or at Week 104
  - Placebo (N=150): 25.3%
  - Infliximab 5 mg/kg (N=147): 17.7%
  - P-value: 0.098

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 (ie, AZA, 6-MP, or MTX).

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

- Proportion of Subjects (%)
  - Placebo (N=150)
  - Infliximab 5 mg/kg (N=147)

- Endoscopic Recurrence only Based on Endoscopic Criteria (i.e., Rutgeerts score ≥12)
  - Placebo: 51.3%
  - Infliximab: 22.4%

- Endoscopic Recurrence with Treatment Failure Rule and Other Data Handling Rules Applied
  - Placebo: 60.6%
  - Infliximab: 30.6%

P < 0.001†

†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).

Subjects with Central Endoscopic Results (Rutgeerts Score i0 vs ≥i3) Prior to or at Week 76

Conclusion and Title of the Publication

Infliximab reduces endoscopic, but not clinical, recurrence of Crohn’s disease after ileocolonic resection

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

**Primary Outcome:** 18 mos Endoscopic Recurrence

**Randomization:** Group 1 had a 6 month colonoscopy (if CD then escalate rx) vs Group 2 no 6 month colonoscopy

All patients received postop metronidazole x 3m

**Low Risk for recurrence:** No additional Medication

**High Risk:** Thiopurine or Adalimumab if intolerant or previously failed thiopurine

49% vs 67% Endoscopic Recurrence at 18 Months in Active vs Standard Care Pts

By Scoping at 6 months and Intensifying Rx: 18% Lower Rate of Endoscopic Recurrence

6-month Endoscopic Recurrence in Thiopurine- and Adalimumab-treated Patients

*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

Does the type of anti-TNF “matter” after surgery?

Infliximab or Adalimumab
Adalimumab or Infliximab for the Prevention of Early Postoperative Recurrence of Crohn Disease: Results From the ENEIDA Registry

• Retrospective, included pts started on an antiTNF within 3 months

• No difference between anti-TNFs for recurrence

Canete et al IBDj 2019
Ultimate Question: When Is it Too Late to Start a Biologic and When Is it Just Right?

Too late = irreversible damage

- **Histologic**: Within 1 week
- **Endoscopic**: 70-90% by 1 yr
- **Radiologic**: Tissue damage
- **Clinical**: 30% 3 yr, 60% 5 yr
- **Surgical**: 50% by 5 yrs

So... the question still remains: How should we manage a Crohn’s disease patient who recently had surgery?

Are there better evidence-based data or guidelines to help us?
American Gastroenterological Association Technical Review of the Management of Crohn’s Disease after Surgical Resection

...this AGA Technical Review informed...
American Gastroenterological Institute Guideline for the Management of Crohn’s Disease after Surgical Resection
#1: The AGA recommends “early pharmacological prophylaxis over endoscopy-guided pharmacological treatment”

Conditional recommendation, very low quality of evidence

- **Histologic**: Within 1 week
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#2: “In patients with surgically induced remission of CD, the AGA suggests using anti-TNF therapy and/or thiopurinines over other agents”

*Conditional recommendation, moderate quality of evidence*

#3: “In patients with surgically induced remission of CD, the AGA suggests **AGAINST** using mesalamine (or other 5-aminosalicylates), budesonide or probiotics

*Conditional recommendation, low quality of evidence*

#4: The AGA suggests routine postoperative endoscopic monitoring at 6 to 12 months over no monitoring

*Conditional recommendation, moderate quality of evidence*

**Colonoscopy 6-12m**

- **Histologic**
  - Within 1 week

- **Endoscopic**
  - 70-90% by 1 yr

- **Radiologic**
  - Tissue damage

- **Clinical**
  - 30% 3 yr
  - 60% 5 yr

- **Surgical**
  - 50% by 5 yrs

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**Surgery**

#5: Pts with asymptomatic endoscopic recurrence, the AGA suggests initiating or optimizing anti-TNF and/or thiopurine therapy over continued monitoring alone

*Conditional recommendation, moderate quality of evidence*

- **Histologic**
  - Within 1 week

- **Endoscopic**
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- **Surgical**

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So... after all of these years...

...my approach to postoperative Crohn’s disease has changed little with TWO small exceptions:

1) Approach to anastomotic ulcerations
2) I don’t use monotherapy 6MP/AZA
Anastomotic “Ring” of Ulcers: Is This CD? What’s the Score?
Anastomotic Ulcers After Ileocolic Resection for Crohn's Disease Are Common and Predict Recurrence.

i2a = Crohn’s but I treat this as i0. What Happens to the Anastomosis Over Time?

Anastomotic stricture
My Approach: High vs Low Risk

Low

No Meds

Colonoscopy 6 months post-op

No Recurrence

Colonoscopy every 1-3 yrs

Recurrence

Immunomodulator or anti-TNF

High

*Anti-TNF monotx

Colonoscopy 6-12 months post-op

No Recurrence

Colonoscopy every 1-3 yrs

Recurrence

↑ anti-TNF or Δ biologics

1st surgery, NOT for penetrating ds (fistula above stricture?)

Penetrating ds (no stricture), > 2 surgeries

*Mono with TDM or combo if antibodies

Other biologics?

Antibiotics?
Take-Home Points

• Recurrence of postoperative Crohn’s disease is common
• Penetrating disease and recurrent surgery are predictors of recurrence
• Smoking is the only modifiable environmental factor
• Anti-TNF therapy may prevent recurrence in high-risk patients
• Vedolizumab and Ustekinumab do not increase postop complications. IIS underway with postop Vedo.
• Small bowel US and fecal calprotectin may be noninvasive ways to monitor postoperative recurrence
• Microbiome-environment-genetic studies reveal insight into postop CD and other Immune mediated diseases
Thank you!
Yes,....... I’m still a fan
My “Old” Algorithm

**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*