INFLIXIMAB FOR PREVENTION OF POST-OPERATIVE CROHN’S DISEASE RECURRENCE:
THE PREVENT TRIAL

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Objectives

• Discuss the current medical management of Crohn’s disease following surgery
• Review the results of the PREVENT trial
• Discuss the place of infliximab in the post-operative management of Crohn’s disease
Surgery is Not a Cure:
CD Recurrence Following Resection

At least 50% of patients require surgical treatment in the first 10 years of disease and approximately 70–80% will require surgery within their lifetime.\footnote{Rutgeerts et al. (1990) Gastroenterol;99:956-963; \textsuperscript{2}Carter et al. Gut 2004;53:V1–16}

The post-operative clinical course is predicted by the severity of endoscopic lesions during the first year after resection.
Management of Post-operative CD Options

- No therapy
  - clinical assessment only
  - endoscopic / radiologic / biomarker follow-up
- 5-ASA
- Antiobiotics (metronidazole / ornidazole)
- Thiopurine analogs
- Anti-TNF agents
Anti-TNF Therapy for Prevention of Post-operative CD Recurrence: Infliximab vs Placebo

8 patients (3 IFX; 5 placebo) had received 1 – 4 doses of IFX prior to surgery

PREVENT TRIAL

- Prospective, Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial Comparing REMICADE® (infliximab) and Placebo in the Prevention of Recurrence in Crohn’s Disease Subjects Undergoing Surgical Resection Who Are at an Increased Risk of Recurrence

- study aim - to assess combined endoscopic and clinical outcome over 76 weeks of treatment in patients at increased risk of recurrence
Increased Risk of CD Recurrence: Criteria

- Qualifying surgery was 2nd operation in past 10 years
- Qualifying surgery was 3rd (or more) operation in past 10 years
- Qualifying surgery was for penetrating complication of CD
- Any history of fistulizing CD provided it was not active in 3 months prior to study
- Cigarette smoker and unable or unwilling to stop
**PREVENT: STUDY DESIGN**

Visits

Week 0
- Randomization (within 45 days of surgery)
- PBO (n = 150)
- 5 mg/kg q8w* (n = 147)
  - **No IFX induction dosing was used**

+ Symptoms + endoscopy

Week 76
- Primary endpoint (clinical recurrence)

Week 104
- Database Lock (week 104)
- IFX 5 mg/kg q8w
- IFX 10 mg/kg q8w

Week 208
- Final Evaluation (Week 208)

**Early Study Termination**

**Regueiro M, et al. DDW 2015, Abstract 749**
**PREVENT Study: Baseline Demographics**

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>Placebo (n = 150)</th>
<th>Infliximab (n = 147)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender, n (%)</td>
<td>81 (54%)</td>
<td>77 (52%)</td>
</tr>
<tr>
<td>Caucasian, n (%)</td>
<td>138 (92%)</td>
<td>138 (94%)</td>
</tr>
<tr>
<td>Disease duration (yrs), median</td>
<td>3.3</td>
<td>6.5</td>
</tr>
<tr>
<td>CDAI, median</td>
<td>109.5</td>
<td>102.5</td>
</tr>
<tr>
<td>Prior intra-abdominal surgeries, N</td>
<td>150</td>
<td>146</td>
</tr>
<tr>
<td>0</td>
<td>91 (60%)</td>
<td>79 (54%)</td>
</tr>
<tr>
<td>1-2</td>
<td>51 (34%)</td>
<td>63 (43%)</td>
</tr>
<tr>
<td>&gt;2</td>
<td>8 (5%)</td>
<td>4 (2%)</td>
</tr>
<tr>
<td>CD medication at baseline*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Corticosteroids (excluding budesonide)</td>
<td>4 (3%)</td>
<td>10 (7%)</td>
</tr>
<tr>
<td>Immunosuppressant, n (%)</td>
<td>88 (59%)</td>
<td>85 (58%)</td>
</tr>
<tr>
<td>Aminosalicylate, n (%)</td>
<td>101 (67%)</td>
<td>100 (69%)</td>
</tr>
<tr>
<td>History of Anti-TNF use, n (%)</td>
<td>30 (20%)</td>
<td>37 (25%)</td>
</tr>
</tbody>
</table>

- Antibiotics not permitted
- Cholestyramine was permitted

Regueiro M et al. DDW 2015, Abstract 749
# Summary of Risk Factors for Recurrence of Active CD in Randomized Subjects

<table>
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<tr>
<th>Patient characteristics</th>
<th>Placebo (n = 150)</th>
<th>Infliximab (n = 147)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized</td>
<td>150</td>
<td>147</td>
</tr>
<tr>
<td>Subjects with risk factor</td>
<td>150</td>
<td>146</td>
</tr>
<tr>
<td>Qualifying surgery was 2\textsuperscript{nd} operation in past 10 yrs</td>
<td>30 (20%)</td>
<td>31 (21%)</td>
</tr>
<tr>
<td>Qualifying surgery was 3\textsuperscript{rd} (or more) operation in past 10 yrs</td>
<td>12 (8%)</td>
<td>14 (10%)</td>
</tr>
<tr>
<td>Qualifying surgery was for penetrating complication of CD</td>
<td>106 (71%)</td>
<td>98 (67%)</td>
</tr>
<tr>
<td>Any history of fistulizing CD provided not active in 3 months prior to study</td>
<td>12 (8%)</td>
<td>16 (11%)</td>
</tr>
<tr>
<td>Cigarette smoker and unable or unwilling to stop</td>
<td>37 (25%)</td>
<td>38 (26%)</td>
</tr>
</tbody>
</table>

Regueiro M et al. DDW 2015, Abstract 749
IFX for Prevention Recurrence in CD Following Ileocolonic Resection

Presence of Clinical and Endoscopic Recurrence at Week 76

- Clinical recurrence†: P = 0.097
- Endoscopic recurrence (i2-i4): P = 0.001
- Severe endoscopic recurrence (i3-i4): P < 0.001

* CDAI ≥ 200 or 70-pt increase, endoscopic recurrence or complication
† Smoker, B2 or B3 disease or > 1 operation: ~30% > 1 risk factor
** No induction dosing was used

Regueiro M et al. DDW 2015, Abstract 749
PREVENT Study: Conclusions

- Primary endpoint (clinical & endoscopic recurrence not met) but trend toward reduced rate on IFX
- Endoscopic recurrence reduced by approximately half in IFX group and similar to prior study results
- No new safety signals
PREVENT Study: Discussion

- clinical recurrence overestimated leading to underpowered study
- follow-up may not be long enough to see clinical impact
- no loading dose
- no therapeutic drug monitoring
- need to differentiate IFX naïve versus experienced patients
- impact of combination therapy
- definition of ‘increased risk’ of recurrence may not be adequately identifying very high risk patients and may result in overtreatment
- role of early endoscopic evaluation not assessed
- required duration of treatment not assessed
PREVENT Study: Incorporating it into practice

- not all patients require infliximab (anti-TNF therapy) after surgery
- use risk stratification to identify high risk patients
  - high risk of recurrence
  - high risk of bad outcome of recurrent disease
- consider infliximab (anti-TNF therapy) in high risk patients