Value of Fecal Calprotectin and CRP in monitoring IBD

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Inanda IBD Meeting

25/03/2017
Disclosures

• Nil
Key Cornerstones

• Initial evaluation and risk stratification
• Setting the treatment goals
• Evidence-based use of available treatment options
• Objective re-evaluation: treatment target reached
• Optimizing treatment (**biomarkers**, TDM)
Evolution of treatment goals

- Clinical Remission
- Endoscopic Remission
- Histological Remission
- Biochemical Remission (CRP and fecal calprotectin)
- Remission on cross-sectional imaging
- PRO Remission

Panaccione et al Infla Bowel Dis 2013
Why Mucosal healing?

- Lower relapse rate
- Fewer hospitalization
- Better QoL
- Decreased need for surgery
- Lower postoperative recurrence
- Reduced CRC risk in UC
- Steroid sparing
- Mucosal lesions predict relapse after anti TNF withdrawal

Peyrin Biroulet L et al J Crohn’s Colitis 2011
Rutgeerts P et al Gastroenterology 1990
Patient expectations

- Symptom free
- Normal QoL
- Uninterrupted school/work
- Normal social/sex life
- No unsightly scars/stoma

Gastroenterologist goals

- Deep remission
- Avoid hospitalization and surgery
- Prevent complications
- Minimize “bowel damage”
- No drug toxicity
Monitoring: Knowing When to Say When

27 yo male (A2), Brother CD, with significant weight loss, with pan-enteric (L3+L4), inflammatory (B1) Crohn’s Disease.

CRP <1 in May 2013
Then 21 in July 2013.

CRP = 21

1 year to induce deep remission?
Monitoring and “Window of Opportunity”

Cleynen I et al Lancet 2016;387:156-67
Monitoring avoids “missed opportunity”

Missed opportunities:
1. Top down therapy
2. Start anti-TNF therapy instead of steroids in July 2013
3. Act on high calprotectin in September 2013
Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE): Determining Therapeutic Goals for Treat-to-Target

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STRIDE

STRIDE Consensus: Treatment goals in CD & UC

• Target is a combination of
  – **Clinical/PRO remission**-resolution of abdominal pain & normalization of bowel habits
  – **Endoscopic remission** resolution of findings of inflammation on cross-sectional imaging

STRIDE Consensus: Treatment goals in CD

• Adjunctive measures of disease activity but are not a target include:
  – CRP
  – Fecal calprotectin

• Measures of disease activity that are not a target:
  – Histology
  – Cross-sectional imaging

Disease monitoring

• **Symptoms ≠ Active inflammation**
  – NB: stenosis, IBS, Bile acid diarrhea
  – 20% of CD and UC patients have symptoms in absence of inflammation

• **NO symptoms ≠ Absence of mucosal lesions**
  – NB: CDAI do not correlate well with endoscopic activity

• **Normal mucosa ≠ No disease activity**
  – NB: transmural and extramural complication

Peyrin-Biroulet L et al Gut 2014;63:88-95
Monitoring disease severity
Objective re-evaluation

### Endoscopy/imaging
- Colonoscopy/ileoscopy/Enteroscopy/CE
- MR enterography/CT enterography
- Transabdominal Doppler/contrast enhanced ultrasonography

### Biomarkers
- CRP
- Fecal calprotectin
Desirable attributes of “IDEAL” biomarker in IBD

- Non-invasive
- Convenient
- Rapid
- Reproducible
- Inexpensive
- Responsive
- Well defined threshold
- Differentiate organic from functional
- Grades severity of inflammation
- Predicts and measures response to therapy
- Monitors and predicts relapse
- Monitors for post-operative recurrence

Sands B, Gastroenterology, 2015;149:1275-1285
Serum CRP in CD

- Acute phase protein produced by the liver (and mesenteric adipocytes in CD) in response to inflammation stimulated by cytokines such as IL-6, TNF-α and IL-1β.
- Single nucleotide polymorphisms (SNPs) reported within various regions of the CRP gene (as well as regulating cytokine genes), which may affect baseline or stimulated CRP production.
- 25% of patients with demonstrable activity of CD on endoscopy do not express CRP above the normal threshold.

Peyrin-Biroulet L et al Gut 2012
Vermeire S et al Inflamm Bowel Dis 2004
Clinically active Crohn's disease in the presence of a low C-reactive protein

- Patients were prospectively recruited over 12 years in Brisbane IBD.
- Subjects in the low CRP group was <10 mg/l.
- Active disease was defined as CDAI > 200.

Florin TH et al Scand J Gastroenterol 2006; 41:306-11
Clinically active Crohn's disease in the presence of a low C-reactive protein

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (CRP &lt; 10mg/L)</th>
<th>Group 2</th>
<th>P values</th>
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<tbody>
<tr>
<td>Number</td>
<td>22</td>
<td>201</td>
<td></td>
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<tr>
<td>Pure ileal disease</td>
<td>95%</td>
<td>53%</td>
<td>0.01</td>
</tr>
<tr>
<td>Lack of pure colonic disease</td>
<td>0%</td>
<td>24%</td>
<td>0.01</td>
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<tr>
<td>BMI (significantly lower)</td>
<td>20.3</td>
<td>25.0</td>
<td>0.006</td>
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</table>

Conclusions:
Patients with CD and a persistently low CRP in the face of active disease were characterized by an almost pure ileal disease distribution and a low BMI, compared to those with a raised CRP. Despite the abnormally low BMI, fat wrapping was noted in the majority of low CRP patients undergoing ileal resection.

Florin TH et al Scand J Gastroenterol 2006; 41:306-11
Baseline CRP predicts response to anti-TNF in CD-ACCENT 1

- 45% of patients with baseline CRP ≥ 7mg/L vs. 22% with CRP< 7mg/L maintained remission (p=0.012).
- Patients with an elevated baseline CRP level that did not normalize by week 14 were less likely to maintain remission through the remaining 40–week study period compared with patients whose CRP level had normalized at week 14.

Figure 3 | Kaplan–Meier analysis of the proportion of patients treated with infliximab who maintained response or remission between week 14 and week 54 according to whether their elevated CRP at baseline had dropped by week 14 to < 0.5 mg/dL (fixed line) or remained elevated (> 0.5 mg/dL, dotted line) [analysis restricted to patients with CRP > 0.5 mg/dL at baseline who were in response (n = 158) or remission (n = 107) at week 14].

Fecal calprotectin in CD

• 60% cytosolic protein mostly contained in neutrophil granulocytes
• High specificity and sensitivity (93-100%)
• Quantitative, non-invasive, stable
• Marker of biochemical and mucosal activity in CD

D’Haens et al Inflamm Bowel Dis 2012
Disease activity and biomarkers in CD

<table>
<thead>
<tr>
<th></th>
<th>IL-6</th>
<th>Calprotectin</th>
<th>Lf</th>
<th>CDAI</th>
<th>SES-CD</th>
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<tr>
<td>hsCRP</td>
<td>0.65</td>
<td>0.47</td>
<td>0.52</td>
<td>0.16</td>
<td>0.46</td>
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<tr>
<td>IL-6</td>
<td>0.45</td>
<td></td>
<td>0.55</td>
<td>0.15</td>
<td>0.43</td>
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<tr>
<td>Calprotectin</td>
<td></td>
<td></td>
<td>0.76</td>
<td>0.23</td>
<td>0.45</td>
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<tr>
<td>Lactoferrin</td>
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<td></td>
<td></td>
<td>0.19</td>
<td>0.48</td>
</tr>
<tr>
<td>CDAI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.15</td>
</tr>
</tbody>
</table>

NOTE. Coefficients in bold are significant at the 0.05 level.
Evidence from the STORI?

- STORI (infliximab discontinuation in Crohn’s disease patients in stable remission on combined therapy with immunosuppressors)
- Factors independently associated with time to relapse:
  - hsCRP level $\geq 5$ mg/L
  - Fecal calprotectin $\geq 300\mu g/g$
  - Leukocyte count $\geq 6 \times 10^9/L$ & Hb $\leq 145$ g/L
  - Male sex
  - No previous surgical resection

Figure 2. Kaplan-Meier time-to-relapse curve of the 115 included patients. The median ± SE follow-up time was 28 ± 2 months. There were 52 patients with confirmed relapse. The median time to relapse was 16.4 months.
Calprotectin predicts relapse in CD

Louis E et al Gastroenterology 2012;142:63-70
The STORI with CRP and fecal calprotectin

• CRP ≤5mg/L can predict mucosal healing with a sensitivity of (70%), low specificity of (40%).
• Fecal calprotectin 250mg/g more effective than CRP at predicting mucosal healing sensitivity (80%), specificity(50%).
• The combination of these 2 markers may further improve accuracy

Louis E et al Gastroenterology 2012;142:63-70
How about Monitoring in postoperative CD

- Half of CD patients require surgery with 10 years after diagnosis
- Endoscopic recurrence within 1 year after surgery is 35%-85%
- Endoscopic recurrence precedes clinical recurrence with approx. 1 year
- ECCO recommends endoscopic monitoring 6-12 months after surgery

Solberg IC et al Clin Gastro Hepatol 2007
Rutgeerts P et al Gastroenterology 1990
Annese V et al J Crohn’s Colitis 2013
POCER the trial?

Randomisation
- Risk stratification
  - Low or high
- Surgery
  - Curative resection

Risk stratification
- Low or high
- Surgery
  - Curative resection

Surgery
- Curative resection

Endoscopic intervention
- 6 month colonoscopy
  - Step-up treatment if recurrence

18 month colonoscopy
- Primary endpoint endoscopic recurrence

De Cruz et al
- Lancet 2014
POCER trial sub-analysis

Endoscopic remission vs recurrence at 6 & 18 months
Matched endoscopy and FCP <300μg/g

Wright EK et al Gastroenterology 2015;148:938-947
Calprotectin and disease progression

NB: Measuring the calprotectin helps decide on magnitude of inflammatory burden given the disconnect with symptoms

******FC monitoring gives enough to help you decide the next step in therapy

Kennedy NA et al ECCO 2012 Poster P250
Tight monitoring

Mild disease
- Corticosteroids / Budesonide

Moderate disease
- EEN or CS + AZA
- +risk factors

Severe disease
- Anti-TNF+ AZA
- -risk factors

Anti-TNF+ AZA

Corticosteroids / Budesonide
Biomakers in UC

• CRP
  – Reduction in CRP corresponds with response to treatment
  – CRP (and albumin) is predictive of colectomy
  – Correlation of CRP levels with mucosal healing is modest
  – ASUC on day 3, CRP > 45mg/L to decide for IFX/CSP

• Fecal calprotectin
  – Correlates with response to induction therapy
  – Is predictive of LOR to maintenance treatment
  – Correlates well with mucosal healing

Henriksen M et al Gut 2008
Cacheux W et al Am J Gastroenterology 2008
Take Home Messages

• Biomakers reflect residual intestinal inflammation.

• Biomakers **facilitate** the monitoring of a patient rather than being a target for treatment *per se*.

• Failure of CRP & FC normalization should prompt further endoscopic evaluation, irrespective of symptoms.
Take Home Messages

• Be aware of potential missed opportunities
• Remember 25% in CD do not express CRP above the normal threshold.
• There is value to monitor using both CRP and FCP
• Close monitoring......and act on the results of monitoring
Thank You