Biomarkers in Inflammatory Bowel Disease

Gauree Gupta Konijeti, MD, MPH
Division of Gastroenterology
Director, Inflammatory Bowel Disease Program
Scripps Clinic Torrey Pines
La Jolla, CA

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Biomarkers in IBD: Overview

• What are biomarkers?
• Available biomarkers: stool tests, blood tests
• Uses and limitations
Therapeutic Goals in IBD

- To get our patients feeling well
- To keep our patients feeling well
- To get our patients OFF of prednisone

Courtesy of Dr. Corey Siegel
Therapeutic Goals in IBD

<table>
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<th>Short Term</th>
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<td>Clinical Remission</td>
<td>Endoscopic Remission</td>
<td>Normalize Quality of Life</td>
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Therapeutic Goals in IBD

Short Term

- Clinical Remission
- Endoscopic Remission
- Normalize Quality of Life

Long Term

- Decrease Flares
- Decrease Hospitalizations
- Prevent Complications
- Maintain Healing
What are Biomarkers?

• Biomarker = an objectively measured characteristic that can be an indicator of something normal (biological), something abnormal (pathogenic), or response to intervention

• Roles of biomarkers
  – Diagnosis
  – Disease monitoring
  – Prognosis
  – (Staging)

• Avoid invasive testing (and time/cost)

Adapted from Atkinson, Clin Pharm Ther 2001
How can biomarkers be used in IBD?

• Aids in the initial diagnosis of IBD
• Distinguish Crohn’s disease from ulcerative colitis
• Predict disease behavior/complications
• Assess efficacy of therapy
• Monitor response to therapy
• Assess or predict relapse
• Predict need for surgery
What Biomarkers Do We Have?

• Stool tests
  – Fecal calprotectin
  – Fecal lactoferrin

• Blood tests
  – High sensitivity c-reactive protein (CRP)
  – Antibodies: pANCA, ASCA, others
What Biomarkers Do We Have?

• Stool tests
  – Fecal calprotectin
  – Fecal lactoferrin

• Blood tests
  – High sensitivity CRP
  – Antibodies: pANCA, ASCA, others

• The ideal biomarker should be... easy to perform, noninvasive (or microinvasive), rapid, reproducible, and cheap!
Stool Calprotectin

• Protein found in our inflammatory cells (neutrophils)
• Indirect way to measure inflammation in the bowel lining (mucosa)
• Stable in stool for up 1 week!

Tibble, Gut, 2000; Von Roon, AJG, 2007
Uses of Stool Calprotectin

• Aid in diagnosis of IBD
  – In general, a level greater than 50 mcg/g can help distinguish IBD from functional bowel disorders (eg, irritable bowel syndrome)
  – Cut off (eg, 50 vs 100 mcg/g) depends on lab test used
  – Does not replace endoscopy or imaging!

• Monitoring disease activity
  – Is the inflammation decreasing and staying down???
  – Correlates better with inflammation in the colon than small intestine
  – Correlates better with findings on endoscopy than symptoms
  – May be slightly better in ulcerative colitis than Crohn’s
Uses of Stool Calprotectin

- Predicting disease relapse
  - Your IBD has been controlled... do your new symptoms suggest disease relapse, or something else?
  - Using higher cutoffs in studies (100-150 mcg/g)
  - Ulcerative colitis: Slightly more than 80% UC relapsers will have an elevated fecal calprotectin
  - Can predict postoperative recurrence in Crohn’s disease

- Summary
  - Aid in diagnosis of IBD
  - Monitoring IBD activity
  - Predicting relapse on therapy or postoperatively
Other Stool Biomarkers

- **Fecal lactoferrin**
  - Another protein found in our immune cells
  - Stable in feces as well
  - Slightly inferior test characteristics to calprotectin

- **Stool tests in general...**
  - Both calprotectin and lactoferrin are still better alone than blood tests for gut inflammation
  - Also can be elevated in cancer, NSAID damage, celiac disease, microscopic colitis
  - Better for colonic disease than small intestinal disease
  - Tell us more about degree of inflammation rather than extent of disease
Blood tests: CRP

• High sensitivity C-reactive Protein (CRP)
• Nonspecific acute phase protein in our blood → goes up with inflammation
  – ESR (erythrocyte sedimentation rate) not as “acute”

• Uses:
  – Help to distinguish IBD from IBS
  – Assess disease activity (UC>CD)
  – Predict relapse while on therapy, or if going to withdraw therapy
  – Predict response to therapy and need for colectomy in hospitalized patients with severe UC

Poulis, Eur J Gastroenterol Hepatol 2002; AJG 2010; AJG 2007
CRP in Severe Ulcerative Colitis

- CRP in this setting can provide prognosis
- Patients with severe ulcerative colitis admitted to hospital

Travis, Gut, 1996
CRP in Severe Ulcerative Colitis

• CRP in this setting can provide **prognosis**
• Patients with severe ulcerative colitis admitted to hospital
• Day 3 of IV steroids
  – >8 stools per day OR
  – 3-8 stools per day and CRP>45
• Give rescue therapy (infliximab or cyclosporine)

85% risk colectomy

Travis, Gut, 1996
Blood tests: CRP

Considerations:

– Some patients with Crohn’s disease never have an elevated CRP
– Clinical symptoms and raised CRP more likely to suggest active IBD
– Elevated in other conditions (infection, obesity, cardiac disease, etc)

What about ESR (erythrocyte sedimentation rate)?

– Refers to the rate at which red blood cells settle in 1 hour
– VS CRP: peaks less rapidly, resolves more slowly
– Influenced by anemia, gender, pregnancy
– Less commonly used than CRP

Poulis, Eur J Gastroenterol Hepatol 2002
Blood tests: Antibodies

• Looking for antibodies against environmental or self antigens
• Could be related to IBD but not necessarily
• Typically done now as a panel w/ antibody and genetic markers
• Not everyone with Crohn’s disease or UC has positive antibodies (ranges from 40-80% in studies)
• People without IBD can have positive antibodies too (1-8%)
• **Bottom Line**: Still investigational, typically not covered by insurance.

*So, will it change management?*

Papp, World J Gastro, 2007
Blood tests: Antibodies

- P-ANCA
  - Perinuclear antineutrophil cytoplasmic antibody
  - More common in ulcerative colitis

- ASCA
  - Antibody against the cell wall of Saccharomyces cerevisiae
  - More common in Crohn’s disease
  - May be associated with stenosis or need for small bowel surgery
  - May predict development of Crohn’s after colectomy

Melmed, Gastro 2007
Blood tests: Antibodies

• So many others... ALCA, ACCA, AMCA, OmpC, I2, Cbir1

• Uses in practice
  – Help determine if this is IBD
    • One piece of the assessment
    • Does not replace the history and other diagnostic modalities (imaging, endoscopy, biopsy)
  – Help distinguish type of IBD for Indeterminate Colitis – 50/50
  – May help identify patients at higher risk of complications of IBD, consider more aggressive therapy earlier on

Summary

• Biomarkers for use in IBD include blood tests (CRP, ESR, antibodies) and stool tests (calprotectin, lactoferrin)

• CRP and calprotectin most frequently used
  – Aiding in the initial diagnosis of IBD
  – Assessing baseline/severity of disease
  – Monitoring response to therapy
  – Predicting or assess relapse
  – Before considering removal of combination therapy
  – Predicting need for immunosuppression in severe UC

• If needed, serology to help diagnose and distinguish type of IBD
Thank you for your time!