Should mucosal healing be the Endpoint of Therapy in UC: No

ACG Regional Course
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Remember the Question:
What is the primary outcome of therapy?

Clinical Remission
Vs.
Mucosal healing
NOT
Symptomatic IBD
Vs
Mucosal Healing
What is Mucosal Healing?

- Clinical Trials:
  - Endoscopy score of 0.
  - Endoscopy score of 0-1
  - Absence of ulceration as determined by visual assessment
- Consensus Statement:
  - Restoration of normal mucosal appearance by endoscopy of a previously inflamed region and the complete absence of ulceration and macroscopic and histological signs of inflammation.

Feagan Inflamm Bowel Dis 2011 Oct 29: epub

What is Clinical Remission?

- Ulcerative Colitis
  - Total Mayo Score of < 2 points with no individual subscore >1 point
  - SCCAI <3
- Crohn’s Disease
  - CDAI <150
  - HBI ≤ 4
- Return to baseline health

D’Haens Gastro 2007;132:763–786
Vermiere Clin Gas Hep 2010;8:4:357-63
Mucosal Healing is Good 😊

- Complete endoscopic mucosal healing is associated with lower rates of relapses, steroid use, hospitalization, and surgeries

Other things that seem good and associated with certain positive outcomes

- Having 5 trillion dollars
- Looking like a movie star
- Being an astronaut
Mucosal Healing is a good idea, just not realistic at this point in time 😐

• Unknown cost and acceptance by patients (not $)
  – Risk to benefit ratio
  – What patient feeling well wants to undergo a procedure and step up therapy
    (particularly to one with potential side effects)?
• Problems with this outcome
  – Disconnect between symptoms and mucosal healing
• Not achievable in many patients:
  – Current medical therapy does not achieve complete steroid free remission in the
    majority of patients (clinical trials)
  – The most effective therapies (anti-TNF) cannot achieve mucosal healing in the
    majority of patients and have limited durability of response in a life long disease
• We do not know how to achieve mucosal healing
• We already many examples from other chronic diseases (and
  history) that the “perfect is the enemy of good”

Case Scenario

• 25 M with a new diagnosis of UC
  – Presents with moderate flare
  – Started on 4.8 gm mesalamine
  – 6 weeks later, in remission
  – Lab parameters have normalized
  – Feels great. Promises to be compliant
• Would you do a flex sig on this patient to confirm healing?
• Would you step up therapy in a completely asymptomatic young (or old) patient based on lack mucosal healing on flex sig?
  – Start azathioprine +/- biologic?
  – Expose this patient to potential side effects with no symptomatic gain?

<table>
<thead>
<tr>
<th>Case Scenario</th>
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<tbody>
<tr>
<td>• 25 M with a new diagnosis of UC</td>
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<tr>
<td>– Presents with moderate-severe flare</td>
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<tr>
<td>– Started on infliximab 5 mg/kg 0, 2, 6 and azathioprine 2.5 mg/kg</td>
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<tr>
<td>– 30 weeks later in clinical remission</td>
</tr>
<tr>
<td>– Lab parameters have normalized</td>
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<tr>
<td>– Feels great. Promises to be compliant</td>
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</table>
• Would you do a flex sig on this patient to confirm healing?
• What would your step up be if no MH?
  – Check infliximab levels and increase dose?
  – Check AZA metabolites and increase dose?
  – Switch to alternative TNF or anti-integrin?
  – Colectomy?

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ASCEND I and II Trials: Remission & Response

Treatment Success at Week 6
Pooled Moderate Population

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<thead>
<tr>
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<th>2.4 g/day</th>
<th>4.8 g/day</th>
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<tbody>
<tr>
<td>Remission</td>
<td>15%</td>
<td>20%</td>
</tr>
<tr>
<td>Response</td>
<td>44%</td>
<td>55%</td>
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Mucosal Healing With Delayed-Release Mesalamine in ASCEND I and II Trials (Moderates)

Mucosal healing defined as endoscopy subscore of 0\(\text{\textsuperscript{2}}\) or 1\(\text{\textsuperscript{1}}\)

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<thead>
<tr>
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<th>Week 3</th>
<th>Week 6</th>
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<tbody>
<tr>
<td>Patients With Mucosal Healing (%)</td>
<td>58</td>
<td>65</td>
</tr>
<tr>
<td></td>
<td>68</td>
<td>80*</td>
</tr>
</tbody>
</table>

\(\text{\textsuperscript{2}}\) normal (intact vascular pattern, no friability or granularity)
\(\text{\textsuperscript{1}}\) mild (erythema, diminished or absent vascular markings, mild granularity, friability)

Early Mucosal Healing with Infliximab is Associated with Improved Long-term Clinical Outcomes in Ulcerative Colitis

- **Objective:** ACT 1 and ACT 2 studies evaluating the association of long-term outcomes with endoscopy subscores achieved at Week 8 following a course of induction therapy with infliximab (IFX)

- **Methods:** Subgroup Analyses
  - 728 patients were randomized to treatment: 244 to placebo and 242 each to IFX 5 mg/kg and 10 mg/kg
  - Symptomatic Remission: Mayo stool frequency subscore of 0 or 1 and a Mayo rectal bleeding subscore of 0
  - Clinical remission was defined as a Mayo score of ≤2 points with no individual subscore >1 point.

Results

• Degree of mucosal healing after 8 weeks of IFX was correlated with improved clinical outcomes including colectomy
• “Degree of mucosal healing at week 8 among those in clinical remission did not predict subsequent disease course”
• Among patients with clinical remission at Week 8, endoscopy score of 0 vs. 1 did not predict subsequent colectomy, symptomatic remission, corticosteroid-free remission or sustained mucosal healing

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How does one “achieve” mucosal healing

Do not perform a test if you will not act on the results.

• In open label studies as well as in clinical trials of combination therapy, the majority of patients will NOT achieve complete mucosal healing.

• Patients who are high risk for significant recurrence (post-operative, recurrent flares, active disease) should be monitored carefully and therapy should be optimized.

• However, patients who are in true clinical remission on appropriate therapy we do not known how to push them to mucosal healing.
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We seek the “golden mean”
Recognized throughout history

- Aristotle: avoid excess and deficiency
- Confucius: Better a diamond with a flaw than a pebble without
- Voltaire: “perfect is the enemy of good”
- Shakespeare: “striving to be better, we often mar what is well”
- Pareto principle: 80-20 rule
  - 20% time to complete 80% of task, the last 20% takes 80% of the effort, resulting in diminishing returns, further activity becomes increasingly inefficient

Conclusions

- Mucosal healing is an admirable goal
  - Predictive value of MH requires further testing, particularly in those in clinical remission
  - More effective medical therapy to attain clinical remission AND to attain mucosal healing is needed
- Clinical remission remains the more realistic and palatable endpoint for patients with IBD
- Perfect is the enemy of good