Mucosal healing: does it really matter?

Professor Jean-Frédéric Colombel, New York, USA
Mucosal healing: does it really matter?

Jean-Frederic COLOMBEL

Icahn Medical School at Mount Sinai, New York
THERE ARE KNOWN KNOWNS
THAT IS TO SAY, THERE ARE
THINGS THAT WE NOW KNOW WE DON’T KNOW
BUT THERE ARE ALSO
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THERE ARE THINGS
WE DO NOT KNOW
WE DON’T KNOW
AND EACH YEAR WE DISCOVER
A FEW MORE OF THOSE
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D.Rumsfeld
• In UC, mucosal healing is associated with better outcomes
• The degree of healing influences the outcomes

UC = ulcerative colitis
UC: outcomes at 5-year follow-up according to early response to steroids

* $p<0.05$ vs clinical and endoscopic remission

# $p<0.05$ vs clinical remission ($\pm$ endoscopic remission)

UC: Early Mucosal Healing With Infliximab is Associated With Improved Long-term Clinical Outcomes

Infliximab-treated patients

$P < 0.0001$

Week 30 (ACT 1 and 2)

Endoscopic Score 0 (n=120)  Endoscopic Score 1 (n=175)  Endoscopic Score 2 (n=114)  Endoscopic Score 3 (n=57)

Week 8 endoscopic score

UC: Early mucosal healing with infliximab is associated with reduced risk of colectomy

### Kaplan-Meier Estimates of Time to Colectomy in Infliximab-Treated Patients

<table>
<thead>
<tr>
<th>Week 8 endoscopy score (n=466)</th>
<th>No. of colectomies</th>
<th>Week 54 colectomy-free probability (%)</th>
<th>p value&lt;sup&gt;b&lt;/sup&gt; (log rank)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 (n=120)</td>
<td>6</td>
<td>95</td>
<td>0.0004</td>
</tr>
<tr>
<td>1 (n=175)</td>
<td>8</td>
<td>95</td>
<td></td>
</tr>
<tr>
<td>2 (n=114)</td>
<td>14</td>
<td>87</td>
<td></td>
</tr>
<tr>
<td>3 (n=57)</td>
<td>10</td>
<td>80</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>Patients randomised to infliximab. Patients who had colectomy or discontinued before week 8 were not included

<sup>b</sup>p value indicates the difference in distributions of time to colectomy among the 4 endoscopy score subgroups

UC = ulcerative colitis

UC: Early mucosal healing with infliximab is associated with reduced risk of infliximab failure

Survival without IFX failure according to the initial endoscopic response to IFX

• In CD mucosal healing is associated with better outcomes
• The relationship between the degree of endoscopic healing and outcomes —is not yet established —may be influenced by treatments
Among patients treated with anti-TNF, the best endoscopic response was associated with highest chances of clinical remission at 1 year (CDAI<150 at w52) in CD: Early mucosal healing is associated with long-term remission (Extend).

\[ p<0.0001 \]

\[ \text{OR 19.6 (95\%CI 4.79-80.2)} \]

CD: Endoscopic healing in CD at year 2 predicts sustained clinical remission (SUTD)

49 patients from SUTD trial underwent colonoscopy at year 2 and were followed-up through year 3 and 4

<table>
<thead>
<tr>
<th></th>
<th>Patients in remission years 3-4 (%)</th>
<th>p-value</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Remission off-GCS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SES-CD = 0 (n=24)</td>
<td></td>
<td>0.036</td>
<td>6.48</td>
<td>1.8-23.4</td>
</tr>
<tr>
<td>SES-CD 1-9 (n=22)</td>
<td></td>
<td>0.032</td>
<td>7.5</td>
<td>1.9-29.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.009</td>
<td>0.148</td>
<td>0.016-1.38</td>
</tr>
<tr>
<td><strong>Remission off-GCS &amp; off-IFX</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>New or active draining fistulae</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SES-CD = 0 (n=24)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SES-CD 1-9 (n=22)</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

CD: mucosal healing at one year is associated with a reduced risk of surgery

IBSEN study: risk of future surgery in patients with mucosal healing at 1 year (n=146)

- Mucosal healing: 83%
- No mucosal healing: 69%

Hazard ratio = 0.42, 95% CI 0.20–0.89; p=0.027

Adjusted for age and disease extent at diagnosis

CD: patients who achieved deep remission* with adalimumab at Week 12 were less hospitalized through week 52 (Extend)

* Deep remission defined as clinical remission (CDAI <150) and complete mucosal healing in EXTEND

CD: patients who achieved deep remission* with adalimumab at Week 12 had better quality of life through week 52 (Extend)

IBDQ remission† at Week 52

* Deep remission defined as clinical remission (CDAI <150) and complete mucosal healing in EXTEND
† IBDQ remission defined as IBDQ score ≥170

• In CD mucosal healing is one of the predictors of relapse after anti-TNF withdrawal

• Mucosal healing does not predict relapse after corticosteroid or azathioprine withdrawal

TNF = tumour necrosis factor
Relapse upon infliximab discontinuation (STORI)

Treated with combined scheduled infliximab+immunosuppressive therapy for at ≥1 year
In stable remission without steroid for >6 months
Factors predicting time to relapse: male gender, surgery, steroids, Hb, WBC, hsCRP, CDEIS

Global and individual curves according to predictive index

<table>
<thead>
<tr>
<th>Index</th>
<th># relapse</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤4</td>
<td>2/19</td>
</tr>
<tr>
<td>=5</td>
<td>10/36</td>
</tr>
<tr>
<td>=6</td>
<td>13/24</td>
</tr>
<tr>
<td>=7</td>
<td>25/28</td>
</tr>
</tbody>
</table>

Global and individual curves according to predictive index

# at risk: 115 102 79 63 51 47 39 27 20 12 9

HsCRP = high-sensitivity C-reactive protein; CDEIS = CD endoscopic index of severity

Relapse after steroid withdrawal according to endoscopic remission

Prospective study in active colonic or ileocolonic CD patients (n=147), treated with prednisolone 1 mg/kg/d. Endoscopic evaluation of those who entered in clinical remission (92%) after 3–7 weeks of treatment, and follow-up for 18 months or until relapse.

Maintained clinical remission on follow-up

Endoscopic remission (n=33)

NO initial endoscopic remission (n=37)

Randomised, double-blind, placebo-controlled, multicentre azathioprine withdrawal trial in CD

Presence of endoscopic lesions (CDEIS 0) or ulcerations was not a predictor of relapse.

<table>
<thead>
<tr>
<th>Time after randomisation (months)</th>
<th>Azathioprine</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>6</td>
<td>0.9</td>
<td>0.9</td>
</tr>
<tr>
<td>12</td>
<td>0.8</td>
<td>0.8</td>
</tr>
<tr>
<td>18</td>
<td>0.7</td>
<td>0.7</td>
</tr>
</tbody>
</table>

Patients at risk (relapses):

<table>
<thead>
<tr>
<th></th>
<th>Azathioprine</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients at risk</td>
<td>40</td>
<td>43</td>
</tr>
<tr>
<td>(relapses)</td>
<td>38 (1)</td>
<td>40 (3)</td>
</tr>
<tr>
<td></td>
<td>34 (2)</td>
<td>35 (7)</td>
</tr>
<tr>
<td></td>
<td>23 (3)</td>
<td>27 (9)</td>
</tr>
</tbody>
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D.Rumsfeld
What is the definition of mucosal healing?

**Crohn’s disease**
- No mucosal ulceration in any of 5 segments
- Absence of mucosal ulceration
- Disappearance of all ulcerative lesions
- CDEIS ≤2, ≤3, ≤4, ≤6
- SES-CD ≤5
- Rutgeerts score ≤i1

**Ulcerative colitis**
- Normal, improved, no change or worse
- Severity of bleeding without considering ulcers
- UC-DAI≤1
- Mayo≤1
- UCEIS < ?

Need for homogenous definition of endoscopic healing
What is the prognostic endoscopic threshold in CD?

<table>
<thead>
<tr>
<th>Mucosal Healing</th>
<th>Surgery Need</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete (n=85)</td>
<td>14.1 (n=12)</td>
</tr>
<tr>
<td>Partial (n=43)</td>
<td>14.0 (n=6)</td>
</tr>
<tr>
<td>No (n=86)</td>
<td>38.4 (n=12)</td>
</tr>
</tbody>
</table>

Endoscopic response at wk 26 predicts corticoid-free remission at wk 50 (SONIC)

Mucosal healing and endoscopic response (defined as a decrease from baseline in SESCD or CDEIS of at least 50%) at week 26 identified patients most likely to be in CFREM at week 50

Mucosal healing and the small bowel?

Before therapy
Mucosal healing and the small bowel?

After therapy

UC: is rectosigmoidoscopy enough to assess mucosal healing?

Proctitis

- Tenesmus, urgency
- Faecal incontinence
- Passage of mucus and fresh blood

Left-sided colitis

- Bloody diarrhoea
- Sometimes proximal constipation

Pancolitis

- Diarrhoea
- Weight loss
- Fever
- Clinically significant blood loss
- Abdominal pain
Colon capsule: next tool for assessing mucosal healing in IBD?

Performances of colon capsule in detecting inflammation with endoscopy as gold standard

<table>
<thead>
<tr>
<th>Diagnosis of active UC lesions</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>True positive, n</td>
<td>68</td>
</tr>
<tr>
<td>False positive, n</td>
<td>5</td>
</tr>
<tr>
<td>True negative, n</td>
<td>15</td>
</tr>
<tr>
<td>False negative, n</td>
<td>8</td>
</tr>
<tr>
<td>Total, N</td>
<td>96</td>
</tr>
<tr>
<td>Sensitivity, % (95% CI)</td>
<td>89 (80–95)</td>
</tr>
<tr>
<td>Specificity, % (95% CI)</td>
<td>75 (51–90)</td>
</tr>
<tr>
<td>Positive predictive value, % (96% CI)</td>
<td>93 (84–97)</td>
</tr>
<tr>
<td>Negative predictive value, % (96% CI)</td>
<td>65 (43–83)</td>
</tr>
</tbody>
</table>

Cl = confidence interval

Ksung J, et al Endoscopy 2011
Confocal endomicroscopy in IBD: the next frontier?

Normal mucosa

Active CD

CDEIS<4 with endomicroscopic activity mucosa

Mucosal healing at endomicroscopy

IBD = inflammatory bowel disease

## Confocal endomicroscopy in IBD

### Table 1 Endomicroscopic grade (Watson grade) for in vivo identification of local barrier dysfunction

<table>
<thead>
<tr>
<th>Grade</th>
<th>Cell shedding</th>
<th>Local barrier dysfunction</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. Normal</td>
<td>Cell shedding confined to single cells per shedding site (e.g., figure 1C or D)</td>
<td>None</td>
</tr>
<tr>
<td>II. Functional defect</td>
<td>Cell shedding confined to single cells per shedding site</td>
<td>Fluorescein signal visible in the intestinal lumen with an intensity the same or brighter than the epithelium or fluorescein plumes out of the epithelium into the lumen (e.g., figure 2D)</td>
</tr>
<tr>
<td>III. Structural defect</td>
<td>Microerosions in any field. Microerosion is defined when the lamina propria is exposed to the lumen with multiple cells being shed per site (e.g., figure 2E)</td>
<td>Fluorescein signal visible in the intestinal lumen with an intensity the same or brighter than the epithelium or fluorescein plumes out of the epithelium into the lumen (e.g., figure 2E)</td>
</tr>
</tbody>
</table>

Kaplan-Meier plot of relapse of IBD patients over 12 months after confocal laser endomicroscopy stratified according to their Watson grade

Is mucosal healing the good target?
(The treat-to-target approach)

- Symptoms
- Inflammation mucosal
- Inflammation transmural
- Inflammation histological
- Inflammation molecular

Damage by treating beyond symptoms
UC: discordance between endoscopy and clinical symptoms
Clinical Response, Remission, and Mucosal Healing at 6 Weeks (vedolizumab)

Induction ITT Population

$\Delta 21.7$  
$11.6, 31.7$

$\Delta 11.5$  
$4.7, 18.3$

$\Delta 16.1$  
$6.4, 25.9$

$P<0.01$

95% CI:

Feagan B et al. DDW 2012
UC: discordance between endoscopic and histological healing (n=103)

Individual Geboes histological scores plotted against Mayo endoscopic scores

Predictors of relapse in UC

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Hazard ratio (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.4(^a) (0.2–0.7)</td>
<td>0.003</td>
</tr>
<tr>
<td>Basal plasmacytosis</td>
<td>4.5 (1.7–11.9)</td>
<td>0.003</td>
</tr>
<tr>
<td>No. of prior relapses</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>1.6(^b) (1.2–1.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Men</td>
<td>0.93 (0.7–1.3)</td>
<td>0.64</td>
</tr>
</tbody>
</table>

\(^a\) Per decade

\(^b\) No significant differences in WBC, Hb, and albumin

CI = confidence interval
WBC = white blood cell count; Hb = haemoglobin

UC: histological remission predicts lower hospitalisation rates

Hospitalisation

### Hazard Ratio and P-values

<table>
<thead>
<tr>
<th>Remission Type</th>
<th>Hazard Ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical remission</td>
<td>0.24 (0.05–1.10)</td>
<td>0.07</td>
</tr>
<tr>
<td>Endoscopic remission</td>
<td>0.53 (0.18–1.56)</td>
<td>0.25</td>
</tr>
<tr>
<td>Histological remission</td>
<td>0.27 (0.07–0.95)</td>
<td>0.048</td>
</tr>
</tbody>
</table>

Severity of inflammation is a risk factor for colorectal neoplasia in UC

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. patients (%)</th>
<th>Odds ratio (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Controls (n=136)</td>
<td>Cases (n=68)</td>
<td></td>
</tr>
<tr>
<td>Colonoscopy inflammation score*</td>
<td>1.89 (0.52)</td>
<td>2.22 (0.78)</td>
<td>2.54 (1.45–4.44)</td>
</tr>
<tr>
<td>Histological inflammation score*</td>
<td>2.05 (0.41)</td>
<td>2.38 (0.56)</td>
<td>5.13 (2.36–11.14)</td>
</tr>
<tr>
<td>Family history of colorectal cancer</td>
<td>18 (14)</td>
<td>7 (12)</td>
<td>1.09 (0.40–2.94)</td>
</tr>
<tr>
<td>Primary sclerosing cholangitis</td>
<td>2 (2)</td>
<td>4 (6)</td>
<td>4.00 (0.73–21.84)</td>
</tr>
<tr>
<td>Mesalamine use</td>
<td>122 (90)</td>
<td>65 (96)</td>
<td>2.38 (0.67–8.54)</td>
</tr>
<tr>
<td>Azathioprine use</td>
<td>37 (28)</td>
<td>12 (18)</td>
<td>0.73 (0.30–1.78)</td>
</tr>
<tr>
<td>Folate supplement</td>
<td>5 (4)</td>
<td>1 (1)</td>
<td>0.40 (0.05–3.42)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>9 (7)</td>
<td>2 (4)</td>
<td>0.43 (0.08–2.23)</td>
</tr>
</tbody>
</table>

*Segmental colonoscopic and histological inflammation was recorded by using a simple score (0, normal; 1, quiescent/chronic inflammation; and 2, 3, and 4, mild, moderate, and severe active inflammation, respectively).

In multivariate analysis, the histologic score was the only risk factor (OR, 4.7; 95% CI, 2.1 – 10.5)

CD: Should we look beyond the mucosa?

Mucosal healing is a too limited target!
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D.Rumsfeld
What needs to be done TODAY

• Validation of significant thresholds for mucosal healing in the colon and the small bowel
• Prospective studies
• Long-term studies with significant endpoints
• Comparing different therapeutic approaches using mucosal healing as a therapeutic goal as compared with clinical symptoms
• In early patients
Current trials that can help answer these questions

**CALM**
- Active moderate/severe CD
- Endpoint: mucosal healing at Week 56
- Tight control of disease activity using stringent criteria (CDAI, steroid use, hs-CRP, faecal calprotectin) vs management using less stringent criteria (CDAI, steroid use)

**REACT 2**
- Active luminal CD (HBI >4)
- Endpoint: CD-related complications at 1 year (hospitalisation for CD-related surgery, or bowel damage not requiring hospitalisation)
- Enhanced care algorithm vs step care algorithm