Mucosal Healing in Crohn’s Disease

Geert D’Haens MD, PhD
University Hospital Gasthuisberg
University of Leuven
Leuven, Belgium
Mucosal Lesions in CD: General Features

- CD can affect the entire GI tract
- CD is a segmental disease
- CD is a transmural disease
  - Mucosal lesions > endoscopic samples
  - Deeply situated lesions > surgical samples
Microscopic Features in CD: Early Lesions

• Early lesions occur in a background of normal mucosa (focal lesions)

• Types
  – Summit lesions: damage of small capillaries and loss of epithelial cells
  – Epithelial patchy necrosis
  – Mucosal microulcerations (loss of up to 6 cells)
  – Aphthoid ulcer
  – Mountain peak ulcer: ulcers at the base of crypts
Crohn’s disease: Microscopic features & Diagnosis

- Epithelial alterations
  - Cytological changes > damage & repair
  - Architectural changes
  - Metaplastic changes

- Inflammatory response
  - Intensity
  - Composition
  - Distribution
Treatment of CD: Is Mucosal Healing Important?

- Prolongs remission duration?
- Prevents complications, eg, stenosis, fistulas, growth failure, and cancer?
- Reduces rate and limits scope of surgical intervention?
- Improves quality of life long term?
- Changes the natural history of the disease?
Healing of the Bowel as Primary Endpoint of Treatment in CD

• ‘Altering the course of IBD is only possible when healing of the bowel is induced and maintained long term’

• Sustained healing could result in avoidance of complications and maintained quality of life

• Candidate drugs for induction of healing:
  • ‘rapid healers’: corticosteroids, infliximab, newer biologicals
  • ‘slow healers’: azathioprine/6-MP, MTX
Endoscopic Healing With Steroids at 7 Weeks in CD

*Among patients with clinical remission, n=131

Steroids: endoscopic healing and risk of clinical relapse

- In endoscopic remission (n=52)*: 92% weaned from pred, 65% relapse at 18 mo
- Not in endoscopic remission (n=80)*: 80% weaned from pred, 65% relapse at 18 mo

*After 3-12 weeks of prednisone (1mg/kg/d)

Effect of budesonide and azathioprine on endoscopic lesions after 12 months (randomised trial)

From Mantzaris et al, DDW 2002
Endoscopic Healing With Azathioprine in CD

Demonstrated after a minimum of 6 months therapy in:

Postoperative recurrent inflammation
Primary colitis and ileocolitis
Randomised, double-blind, placebo-controlled, multicenter azathioprine withdrawal trial in Crohn’s disease

Lemann et al, DDW 2002

Start of azathioprine therapy

≥ 42 months

Randomisation
N=83

Clinical remission prednisone < 10 mg/d

ENDOSCOPY N=45

Azathioprine

18 months

Placebo
Proportion of patients in remission on azathioprine/placebo

Remission (months)
mean ± SE

Azathioprine 17.3 ± 0.5
Placebo 15.9 ± 0.7

Patients at risk (relapses)

0,0 0,2 0,4 0,6 0,8 1,0

0 6 12 18

Months after randomization

(Lémann et al, DDW 2002)
Endoscopic lesions after 42 months of remission on azathioprine

Lémann et al, Gastroenterology, in press
Mucosal healing with infliximab
Crohn’s disease: Healing with Infliximab

before

Week 4
Colon TNF stain

before

Week 4
Colon Icam-1 and LFA-1 stains

(courtesy K. Geboes)
Endoscopic Healing With Infliximab

Ileum Ascending Colon Transverse Colon Descending Colon Rectum

74% 95% 79% 77% 96%

Endoscopic Healing With Infliximab in CD

**Infliximab Maintenance Therapy for CD: ACCENT I**

| **Design:** | • 1-y, multicenter, randomized, double-blind |
| **Patients:** | • N=573  
• Adults with moderately to severely active CD (median CDAI=297) |
| **Treatment:** | • Initial: Single 5 mg/kg infliximab infusion  
• Maintenance regimen: Placebo; 5 mg/kg infliximab, or 10 mg/kg infliximab  
• Episodic retreatment: Patients who lost response; +5 mg/kg over maintenance dose |
| **Endpoints:** | • Clinical response and remission  
• Steroid-sparing efficacy  
• Endoscopic healing |
### ACCENT I: Endoscopic Substudy

**Patients:**
- n=99
- 25 selected European sites
- 2-wk responders and recipients of episodic retreatment

**Endoscopic Assessment:**
- Crohn’s Disease Endoscopic Index of Severity (CDEIS)
- Wk 0, 10, and 54

**Definition of Healing:**
- Mucosal ulceration at Wk 0 and no mucosal ulceration at follow-up
Infliximab: Endoscopic Healing*

*Among Week-2 responders (n=66)

Recurrence of ulcers in the same locations as pre-infliximab ‘over night’
Stenosis as a complication of healing
Complete ileal healing
Infliximab: Endoscopic Healing and Risk of Clinical Relapse

Infliximab: Endoscopic Healing and Reduced Hospitalization and Surgeries

Patients with no healing (n=74)

Patients with healing at 1 visit (10 or 54 wk) (n=16)

Patients with healing at both visits (10 and 54 wk)


*Number per 100 patients
Infliximab: Endoscopic Healing and Reduced Hospitalization

ACCENT I

No healing
n=17
24.3%

Healing at 1 visit
n=16
18.8%

Healing at both visits
n=9
0%
Infliximab: Endoscopic Healing and Reduced Surgeries

Patients Undergoing Surgery (%)

- No healing: 5.4% (n=74)
- Healing at 1 visit: 0% (n=76)
- Healing at both visits: 0% (n=9)
Mucosal healing
Effect of different drugs

% of mucosal “healing”

- Prednisone (Modigliani et al)
- Azathioprine (Mantzaris et al, Lémann et al)
- Budesonide (Mantzaris et al)
- Infliximab (Rutgeerts et al)

Weeks: 6, 10, 52, 250

Y-axis: % of mucosal “healing”
<table>
<thead>
<tr>
<th>Drug</th>
<th>Effect</th>
</tr>
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<tbody>
<tr>
<td>5-ASA</td>
<td>Unknown</td>
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<tr>
<td>Antibiotics</td>
<td>Unknown</td>
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<tr>
<td>Steroids</td>
<td>Limited</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>Yes (slow)</td>
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<tr>
<td>Methotrexate</td>
<td>Yes ?</td>
</tr>
<tr>
<td>Infliximab</td>
<td>Yes (rapid ?)</td>
</tr>
<tr>
<td>Natalizumab</td>
<td>(YES)</td>
</tr>
<tr>
<td>CNI-1493</td>
<td>Yes (rapid)</td>
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</tbody>
</table>
Mucosal Healing in CD: novel agents

- Natalizumab (anti-alpha4-antibody Antegren): currently under study
- Etanercept: little clinical benefit, no endoscopic nor histological changes observed
- Map-kinase inhibitors
NATALIZUMAB (Antegren®) in CD

- Multinational study with 905 pts / 59 in colonoscopy substudy
- 12 sites – N= 42 Antegren 300 mg IV w 0,4 and 8 – N=15 placebo
- Colonoscopy at week 0 and 10
- 50 % reduction in CDEIS with ANT vs 7 % with PLAC
- Ulcer-free pts at week 10: 22 % ANT vs 8 % with PLAC
- Strong correlation histological / endoscopic improvement

Rutgeerts et al., Gastroenterology 2004 (abstr)
**Immunomodulation and healing in Crohn’s Disease**

**Biologicals:**
- Anti-TNF
- Anti-IL12
- Anti-IFN
- etc.

**Small Molecules:**
- MAPK inhibitors (CNI-1493)
- p38 inhibitors
- JNK inhibitors

**Transcription Factor:**
- Corticosteroids
- Thalidomide
Disease Modification in CD: Unanswered Questions

• What are the clinical benefits of mucosal healing?
  – Improved quality of life?
  – Longer duration of clinical remission?
  – Limited need for or scope of surgery?
  – Decreased complications (eg, growth failure)?

• Should therapies that provide mucosal healing be introduced earlier in the disease course?
  – Post diagnosis?
  – Post surgery?

• How will the next generation of therapies perform?