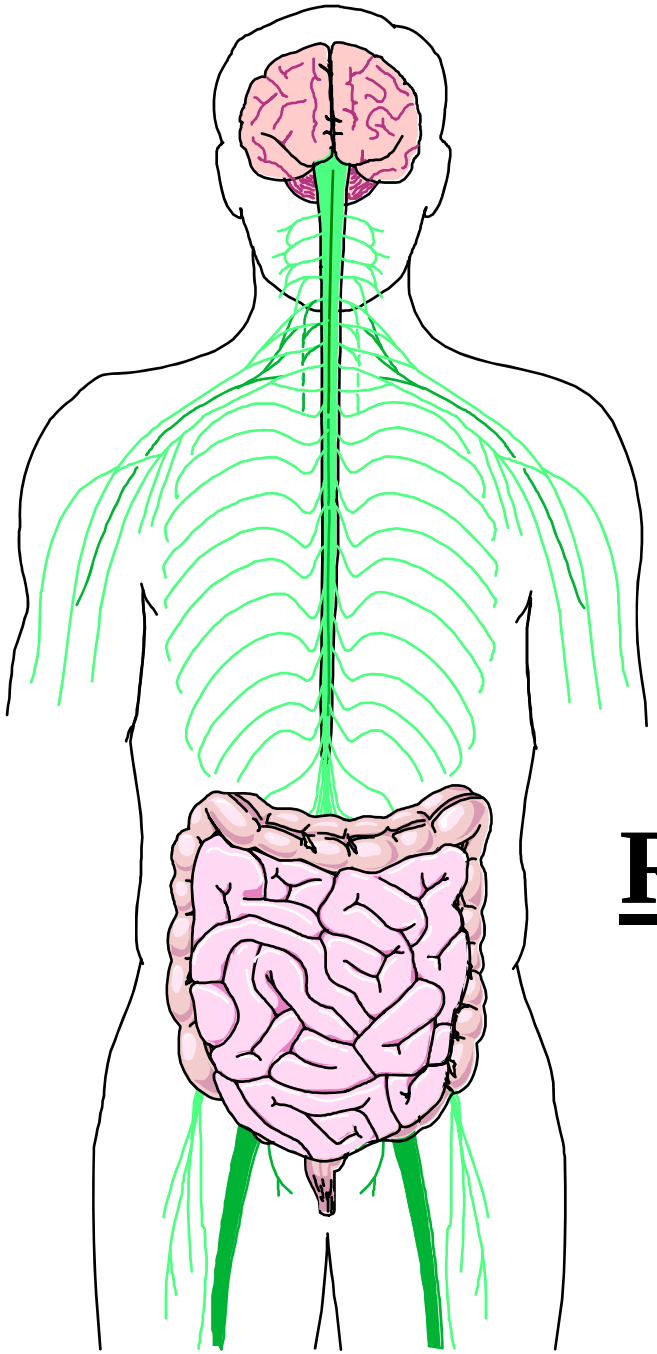

Mucosal Healing or Clinical Endpoints: What is Best?

Richard MacDermott MD

What Endpoints are Important?

1. **Therapy endpoints important to the Patient:**
   - **Clinical symptoms.**
   - **Quality of life**

2. **Therapy endpoints important to the Physician:**
   - **Blood work**
   - **Mucosal healing**

What is Mucosal Healing?

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

Feagan Inflamm Bowel Dis 2011 Oct 29

Evidence from Trials of Biologics in Crohn's Disease with Mucosal Healing as an Endpoint

Year	Agents	Definition of Mucosal healing
1995	Infliximab	Complete or near-complete healing
2004	Infliximab	Complete absence of ulcers seen at baseline
2004	Natalizumab	No ulcers
2008	Infliximab Azathioprine	Complete absence of ulcers in the colon and terminal ileum seen at baseline
2008	Infliximab Azathioprine	No ulcers
2008	Certolizumab	Absence of ulcers CDEIS < 6
2009	Adalimumab	Absence of ulcers

Pineton de Chambrun G Nat. Rev Gastroenterol 2010;7:15-29

Mucosal Healing is Associated With:

- **Prolonged steroid free remission**
- **Fewer hospitalizations**
- **Fewer penetrating complications**
- **Fewer abdominal surgeries**
- **Fewer colectomies**
- **Mucosal healing is associated with significant positive changes in the natural history of IBD**

Why is Mucosal Healing Important?

Mucosal healing correlates better with maintenance of remission than does resolution of symptoms

What are the Problems with Using Mucosal Healing as an Endpoint of Therapy? I

In open label and in clinical trials, the majority of patients do NOT achieve complete mucosal healing

Even the most effective therapies (anti-TNF-Biologics; Combination Therapy) cannot achieve mucosal healing in the majority of patients

Clinical response and remission do not necessarily correlate with mucosal healing

What are the Problems with Using Mucosal Healing as an Endpoint of Therapy? II

IBD patients who are in clinical remission, on therapy, do not need to achieve mucosal healing to feel better

Moreover, should we perform a test, if we will not act on the results?

Do patients, who feel well, want to undergo a procedure and then change therapy (particularly to one with more possible side effects)?

What is Clinical Remission in Trials?

- **Ulcerative Colitis**
  - **Total Mayo Score of < 2 points with no individual subscore >1 point**
  - **SCCAI <3**
- **Crohn's Disease**
  - **CDAI <150**
  - **HBI ≤ 4**
- **Are these Formal Measurements of use in practice?**
- **Clinical symptoms are what counts**

Problems with Clinical Endpoints: Many Causes of Symptoms in Patients

- **Infection**
  - ***Clostridium difficile***
  - **Enteric Pathogens**
  - **Cytomegalovirus**
- **Irritable bowel syndrome**
- **Disease complications**
  - **Strictures**
  - **Fistulae/Abscesses**
- **Complications of small bowel disease**
  - **Bile acid induced diarrhea**
  - **Small bowel bacterial overgrowth**

Ideal Goal is Deep Remission

Deep Remission is resolution for a significant length of time, of one or more objective measures of inflammation (endoscopy, biomarkers, imaging) and also resolution of clinical symptoms

Case One

- **20 Y/O F with Pan UC on infliximab monotherapy, every 8 weeks, for 4 years**
  - **Feels well and is in Clinical Remission**
  - **Surveillance colonoscopy demonstrates healing**
  - **Biopsies: No inflammation**
  1. **How many would continue infliximab?**
  2. **How many would dose intensify infliximab to achieve even better long term control?**
  3. **How many would discontinue infliximab, if patient requests, due to Deep Remission?**

Case Two

- **20 Y/O F with Pan UC on infliximab monotherapy, every 8 weeks, for 4 years**
  - **Worsening symptoms for 6 months**
  - **Colonoscopy demonstrates active disease throughout the colon**

1. **How many would dose intensify infliximab?**
2. **How many would add 6-MP or AZA?**
3. **How many would change therapy?**

Case Three

- **20 Y/O F with Pan UC on infliximab monotherapy, every 8 weeks, for 4 years**
  - **Worsening symptoms for 6 months**
  - **Colonoscopy demonstrates healing in the right, transverse and descending colon, but active disease in the sigmoid colon and rectum**

1. **How many would dose intensify infliximab ?**
2. **How many would add 6-MP or AZA?**
3. **How many would add topical rectal therapy?**

Case Four

- **20 Y/O F with Pan UC on infliximab monotherapy, every 8 weeks, for 4 years**
  - **Feels well and is in Clinical Remission**
  - **Surveillance colonoscopy demonstrates active disease throughout the colon**

1. **How many would dose intensify infliximab ?**
2. **How many would add 6-MP or AZA?**
3. **How many would add topical rectal therapy?**

Use of Mucosal Healing in 2012

- **If patient feels well with normal labs, no need to do a colonoscopy, except for surveillance.**
- **If patient feels well with normal labs, routine surveillance colonoscopy is appropriate. If active disease is found, follow very closely**
- **If significant symptoms and/or lab abnormalities, do colonoscopy. If active disease found, consider change in dose or type of therapy.**
- **Clinical Remission and normal Quality of Life are the most important goals for IBD patients**

Should Clinical Symptoms or Mucosal Healing be the Goal of Therapy in IBD?

Clinical Symptoms

Mucosal Healing