Latest Treatment Updates for Ulcerative Colitis: Evolving Treatment Goals

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Educational Objectives

- Describe the current overall approach to managing ulcerative colitis, including current data on the relationship between mucosal healing and longer-term outcomes
- Identify recent advances in the management of ulcerative colitis
Treatment Goals c.2014

- Induce and maintain remission
  - Mucosal healing
- Prevent complications
  - Disease Related
  - Therapy Related
- Improve quality of life
- Limit surgery?
Evolving Approach to Treating UC

Near Future Approach
- Newer therapies with favorable safety and side effect profiles
- Individualized therapy based on genetics and physiology
- Treatment to hard endpoints such as mucosal healing or surrogates of it
- Disease monitoring to prevent relapse

Current Approach
- Assessment of prognosis
- “Optimization” of azathioprine/6-MP (dose or metabolites)
- Adopt biologic therapy earlier in disease
- Appreciation for the implications of a healed mucosa

6-MP = 6-mercaptopurine
Predictors of Poor Response or Colectomy

- Low serum albumin
- ESR >30 mm/h
- Bandemia
- Prolonged flare
- Active infection
- Hospitalization setting
- Severe endoscopic lesions
- Disease duration
- Stool frequency
- Percentage of bloody stools
- Body temperature >37.5
- Heart rate >90 bpm
- Increased CRP
- Toxic megacolon
- Low hemoglobin <10.5 g/dL

CRP=C-reactive protein.
High-Risk Patients

• Oxford Index identifies patients with a high risk for colectomy
  – Evaluate CRP concentration
  – Evaluate number of bloody bowel movements
• Biomarkers to identify high-risk patients
  – Serum albumin concentration
  – Fecal calprotectin concentration
• Endoscopic disease severity is predictive
• Residual histopathologic inflammation

Oxford Index: >8 stools/day or 3-8/day and CRP >45mg.dL on third day of corticosteroid.
Mucosal Healing as a Surrogate for Longer Term Outcomes

Associated with:

• Better quality of life
• Fewer hospitalizations
• Fewer surgeries
• Longer time to clinical relapse
• Reduction in dysplasia/cancer

Sands, B. ACG-FDA Workshop 2012
Mucosal Healing: ACG Guidelines

• “Newer goals of therapy include the induction and maintenance of mucosal (and histological) healing that are beginning to translate into changing the ‘natural history’ of CD”¹

• “Mucosal healing, a novel end point in CD associated with improved pharmacoeconomic and quality of life outcomes . . .”¹

• [In UC] “long-term mucosal healing may reduce the risk of dysplasia and predicts a better long-term outcome”²

Mucosal Healing Can Impact the Need for Surgery (IBSEN Study)

- Population-based cohort of IBD pts followed 1990-1994 in Norway\(^1\)
- Patients treated with conventional therapies not including biologics\(^1\)
- Among 495 pts available for analysis, *mucosal healing observed at 1 year in 50% (UC) and 38% (CD)*\(^1\)
- *In UC, mucosal healing was significantly associated with:*
  - less inflammation
  - less corticosteroid treatment 5 years after diagnosis\(^1\)
  - fewer surgeries by 5 years\(^1\)
- *When f/u extended to 10 years:*
  - significantly fewer surgeries in patients with mucosal healing at 1 year\(^2\)

Impact of Mucosal Damage on Subsequent Colectomy in Ulcerative Colitis

Patients with compromised mucosa 1 year after diagnosis showed a trend toward more surgeries.

Mucosal Healing in UC

- Impact of mucosal healing on long-term outcomes in ulcerative colitis treated with infliximab: A multicenter experience
  - 48% (30/63 patients) achieved mucosal healing

By multivariate analysis, mucosal healing was the sole prognostic factor associated colectomy-free survival, with an odds ratio of 18.01 (95%CI: 1.58–204.92)

The Majority of IBD Patients in Clinical Remission have Mucosal Inflammation

- Treatment was not changed after the index endoscopy in 88% (n=92) of patients with inflammation
- Treatment was more frequently altered in group B than in group C (24% vs. 4%; p=0.004)
- Two years after the index procedure on follow-up endoscopy, 29% of all patients had endoscopic inflammation, and another 27% had only microscopic inflammation
Treat-to-target approach has been adopted in other therapy areas

**Treatment targets**

**Diabetes**
- <7% HbA1c

**Hypertension**
- BP: 140/90 mmHg (135/80 mmHg for diabetic patients)
- LDL-cholesterol: 70 mg/dL (to lower incidence of cardiac events)

**Rheumatoid arthritis**
- Remission
- Low disease activity

Potential Wider Implications of a Adopting a Treat-To-Target Approach

- Treatment algorithms are based on treatment targets
  - e.g. achieve ‘absence of disease activity’ in 3–6 months in RA

- Frequent monitoring is recommended so that treatment can be optimised
  - e.g. HbA1c monitoring every 3 months in patients with diabetes

- Modification of the target for high-risk patient groups
  - e.g. lower blood-pressure target of 130/80 mmHg in patients with both hypertension and type 2 diabetes
  - Risk of ‘tight target’ in ICU setting

- Early disease states are recognised
  - e.g. pre-hypertension, pre-diabetes

Evolving Goals of Therapy for IBD: Sustained Deep Remission

<table>
<thead>
<tr>
<th>Goal</th>
<th>Clinical Parameters</th>
<th>Outcomes</th>
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<tbody>
<tr>
<td>Response</td>
<td>Improved symptoms</td>
<td>Improved QoL</td>
</tr>
<tr>
<td>Remission</td>
<td>No symptoms</td>
<td>Decreased hospitalisation</td>
</tr>
<tr>
<td>Deep remission</td>
<td>No symptoms Normal labs Mucosal Healing</td>
<td>Avoidance of surgery</td>
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QoL = quality of life
Modified from Panaccione R. Presented at: European Crohn’s and Colitis Organization (ECCO)
Fifth Annual Congress. Prague, Czech Republic; February 2010
# Comparison of Goals

<table>
<thead>
<tr>
<th>Current</th>
<th>Future</th>
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<tbody>
<tr>
<td>– Symptom control (induce and maintain remission)</td>
<td>– Mucosal healing</td>
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<tr>
<td>– Improve quality of life</td>
<td>– Disease modification</td>
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<tr>
<td>– Minimize drug toxicity</td>
<td>– <em>Predictive Biomarkers</em></td>
</tr>
<tr>
<td>– Minimize disease complications</td>
<td>– <em>Molecular/Genetic markers predicting course &amp; therapeutic response</em></td>
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<tr>
<td>– Optimize surgical outcomes</td>
<td>– Find the cause…</td>
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<td></td>
<td>– Eliminate or tolerize to environmental factors</td>
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Sequential Therapies for Ulcerative Colitis

Therapy is stepped up according to severity at presentation or failure at prior step.
Acute Severe (Inpatient) UC Treatment Algorithm

If no or partial response to IV steroids for 3 to 5 days

- IV cyclosporin
- OR
- IV infliximab
- OR
- Colectomy with ileostomy or IPAA

No or partial response

If response, 6-MP or azathioprine

IPPA = ileal pouch-anal anastomosis

Optimize Treatment Regimens

- 6-TGN monitoring for patients receiving azathioprine and 6-mercaptopurine
- Combination therapy with biologics
- Infliximab concentration and HACA monitoring for patients receiving infliximab
- Position novel therapies

HACA = human antichimeric antibody
# Association of 6-TGN Levels and IBD Activity: A Meta-Analysis

<table>
<thead>
<tr>
<th>Study</th>
<th>Odds Ratio (95% CI)</th>
<th>% Weight</th>
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<tbody>
<tr>
<td>Goldenberg 2004</td>
<td>1.47 (0.47, 4.62)</td>
<td>15.8%</td>
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<tr>
<td>Belaiche 2001</td>
<td>1.62 (0.26, 10.23)</td>
<td>8.9%</td>
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<tr>
<td>Achkar 2004</td>
<td>3.80 (1.17, 12.39)</td>
<td>15.3%</td>
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<tr>
<td>Cuffari 2001</td>
<td>11.63 (3.78, 35.72)</td>
<td>16.1%</td>
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<tr>
<td>Gupta 2001</td>
<td>1.65 (0.73, 3.75)</td>
<td>20.7%</td>
</tr>
<tr>
<td>Dubinsky 2000</td>
<td>5.07 (2.62, 9.83)</td>
<td>23.4%</td>
</tr>
<tr>
<td>Overall (95% CI)</td>
<td>3.27 (1.71, 6.27)</td>
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Correlation Between 6-MP/AZA Dose and 6-TGN Concentration

Responders
Non-responders

6-TGN correlates with dose for responders ($P = 0.026$), but not non-responders ($P = 0.5$)

UC SUCCESS: Corticosteroid-free Remission in Early UC

UC SUCCESS: Mucosal Healing in Early UC

Measuring Infliximab and HACA Concentrations in Patients With IBD: Clinical Outcomes

0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%

Detectable HACA

Subtherapeutic concentration

** P < 0.004
* P < 0.016

Increase infliximab
Change anti-TNF

Addressing Anti-TNF Treatment Failure

- Scheduled vs episodic treatment
- Concomitant therapy with immunomodulators
  - Increased serum concentrations
  - Reduced ADAs
- Monitor adherence
- Confirm lack of inflammation
- Therapeutic switching or dose escalation

Causes of Treatment Failure With Anti-TNF Agents

• Poor adherence reported in one-third of patients
• Suboptimal drug concentrations result from pharmacokinetic (PK) differences
  – Weight-based dosing
  – Measure serum concentrations
• Antidrug antibodies (ADAs) production
• Concomitant Infection (C. Diff & CMV)