Managing the Ulcerative Colitis Patient Who is “Resistant” to 5-ASAs

Dose-escalate or Switch?

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Overview

Introduction

• Patient case
• 5-ASAs in the management of ulcerative colitis
• Conclusions
Natural History of UC

- Within 2 years of diagnosis
  - 17% experience colonic hemorrhage
  - 13% experience toxic colitis
- Disease progresses in 54% of patients within 5 years of diagnosis
- 20% to 38% ultimately require proctocolectomy
- Increased risk of colon cancer

UC: Natural History*

*Percent of patients with disease activity, in remission, or having colectomy performed each year after diagnosis

Optimizing Mesalamine Adherence

• If you want to modify the natural history of Ulcerative Colitis increase adherence. The most common reason for a flare is patients discontinue their medications.

• Symptoms of UC are frequently unpleasant and distressing (1)

• Although 5ASA therapy is effective, many patients fail to take their medications as we prescribe, resulting in symptomatic flares (2)

Increasing activity from diagnosis, leading to colectomy or death within 1 year

>4 stools daily and/or daily presence of blood/pus and/or systemic symptoms

≤4 stools daily and/or presence of blood and/or pus in the stools less than daily; no systemic symptoms
Treatment Options for UC

- 5-ASA
- Steroids
- Immune modifiers
  - Thiopurine (azathioprine/6-MP)
- Biologic therapy – TNF
- Cyclosporine
- Surgery
- Alternative/integrative therapies?

5-ASA=5-aminosalicylic acid; 6-MP=6-mercaptopurine; TNF=tumor necrosis factor.
Traditional Approach
• Patients have to “earn” therapy based on severity or failure of other approaches
• Treatment is based on symptom resolution

Evolving Approach
• Assessment of prognosis
• “Optimization” of azathioprine/6-MP (dose or metabolites)
• Earlier adoption of biologic therapy
• Distinction between cyclosporine and infliximab for severe/fulminant UC
• Appreciation for the implications of a healed mucosa

Future Approach
• Individualized therapy based on genetics and physiology
• Treatment to hard endpoints like mucosal healing or surrogates of it
• Newer therapies with favorable safety and side effect profiles
• Appreciation for timing of surgery in the presence of immune suppression

36 y/o man with 20 years of moderate Ulcerative Colitis in clinical remission on Mesalamine 4.8G. Colonoscopy shows moderate UC with ulcerations from anal verge to cecum.

Is the patient really in clinical remission (Normal study)?

Do we treat to mucosal healing when we have achieved clinical remission?
Results from NORMAL study: More patients than gastroenterologists chose to adapt their lives to the accommodate UC, in contrast gastroenterologists aim to optimize therapy and adherence.

Patients reported on average 8 self defined flares a year… this was more than anticipated by gastroenterologists.

Conclusion: On closer questioning, not all of our patients in “clinical remission” are in clinical remission.
In a patient who is in clinical remission or who is content to live with “subclinical” symptoms, how do we best achieve mucosal healing?

Therapeutic options:
- Optimizing mesalamine delivery
- Switching to immunomodulator therapy
- Switching to biologic therapy
- Minimize importance of mucosal healing
There is no evidence to support mucosal healing by switching within the mesalamine class. However, this is the best therapeutic option available.
Once-Daily 1.5 g APRISO Effectively Maintains Remission in Patients With Ulcerative Colitis Who Switch From Different 5-ASA Formulations

Maintenance of remission at 6 months after switching to Apriso (%)

- Apriso (n=322): 78%
- Placebo (n=165): 59%

ITT=intention to treat

Lichtenstein GR et al. ACG Annual Meeting 2008.
Case

• 28 y/o woman with 10 years of mild Ulcerative Colitis symptomatic improvement on Asacol HD 4.8G. Colonoscopy shows mild UC with salt and pepper ulcerations from anal verge to cecum. She wants to discuss becoming pregnant.

• Emphasize importance of achieving clinical remission.

• Discuss pregnancy categories and the importance of adherence strategies during pregnancy.
Key Questions:

• Step up dosage of 5-ASA?
• Switch to another 5-ASA?
• Escalate therapy?
Overview

Introduction

• Patient case

• 5-ASAs in the management of ulcerative colitis
  – Dose escalation
  – Switching

• Conclusions
### UC Guidelines for 5-ASA Formulations

<table>
<thead>
<tr>
<th>5-ASA</th>
<th>Effective Doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfasalazine</td>
<td>4-6 g/d</td>
</tr>
<tr>
<td>Mesalamine</td>
<td>2-4.8 g/d</td>
</tr>
<tr>
<td>Balsalazide</td>
<td>6.75 g/d</td>
</tr>
<tr>
<td>Olsalazine</td>
<td>1.5-3.0 g/d</td>
</tr>
</tbody>
</table>

- Many physicians tend to dismiss 5-ASA therapy before reaching maximum recommended dosages
- One study evaluated the most recent dose of delayed-release mesalamine that was filled prior to each patient’s first dose of immunosuppressive therapy
  - 39% of patients had been taking mesalamine at a most recent daily dose of 2.4 g/d or lower
- Is this practice justified by the evidence?

UC – Therapy of Active Disease

Oral Mesalamine

- % Patients
- 0
- 35
- 70

Improvement
Complete remission

Placebo
1.6 gms
4.8 gms

Dose Escalation in Patients Failing 5-ASAs: Sninsky Study (1991)

• Objective
  – Evaluate efficacy of 2 doses of mesalamine

• Design
  – Multicenter, double-blind, placebo-controlled, randomized

• Patients
  – 158 patients with newly or previously diagnosed active UC

• Intervention (6 weeks)
  – Placebo
  – Mesalamine 1.6 g/d
  – Mesalamine 2.4 g/d

Increasing Dosage of Mesalamine Did Not Improve Remission or Improvement Rates

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Placebo (n=44)</th>
<th>Mesalamine 1.6 g/d (n=44)</th>
<th>Mesalamine 2.4 g/d (n=43)</th>
</tr>
</thead>
<tbody>
<tr>
<td>In remission</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Improved</td>
<td>3 (7%)</td>
<td>12 (27%)</td>
<td>13 (30%)</td>
</tr>
<tr>
<td>Maintained</td>
<td>17 (39%)</td>
<td>12 (27%)</td>
<td>18 (42%)</td>
</tr>
<tr>
<td>Worsened</td>
<td>23 (52%)</td>
<td>19 (43%)</td>
<td>11 (26%)</td>
</tr>
</tbody>
</table>

ASCEND I and II: 6-Week Data

ASCEND 1

Week 6

Overall Improvement (%)

P = .57

ASCEND 2

Week 6

Overall Improvement (%)

P = .036

ASCEND III Trial

- Multicenter, randomized, double-blind, double-dummy, active-controlled trial conducted at 113 sites in 14 countries
- Initial design to determine whether delayed-release mesalamine 4.8 g/day (800-mg tablet) was superior to 2.4 g/day (400-mg tablet) for treatment success at week 6
- While the ASCEND III study was still blinded and recruiting, another delayed-release mesalamine formulation received regulatory approval for both 2.4 g/day and 4.8 g/day for the treatment of mildly to moderately active UC, despite the absence of a dose-response between the 2.4 g/day and 4.8 g/day doses
- The ASCEND III study design was amended (while the study was still blinded and recruiting) to a noninferiority design
- Noninferiority study to demonstrate that delayed-release mesalamine 4.8g/day (800mg tablet) is effective and safe as compared with delayed-release mesalamine 2.4g/day (400mg tablet) in patients with moderately active UC
Results

Baseline characteristics were similar in the 2 treatment groups.

Figure 1. Patient disposition.
Patients (n = 772) with moderately active ulcerative colitis were randomized to treatment and dosed with delayed-release mesalamine 2.4 g/day or 4.8 g/day.
Results

- At week 6, 70.2% (273 of 389) of patients receiving 4.8 g/day (800-mg tablet) achieved treatment success at week 6, compared with 65.5% (251 of 383) of those who received 2.4 g/day (400-mg tablet) (95% CI for 2.4 g/day minus 4.8 g/day treatment success rates, -11.2 to 1.9).

- The comparison of 4.8 g/day to 2.4 g/day for superiority was not significant ($P = .17$).
† Clinical improvement defined as a drop in the Sutherland Index (UC-DAI) ≥3 points from baseline
‡* Remission defined as a Sutherland (UC-DAI) ≤1 with a score of 0 for rectal bleeding and stool frequency and ≥1-point reduction from baseline in sigmoidoscopy score

* p≤0.05; ** p≤0.01; *** p≤0.001; NS = not significant vs placebo

Objective
- Dose-finding study for new 5-ASA formulation with combined slow and delayed-release properties

Design
- Randomized, double-blind, multicenter

Patients
- Active UC (CAI 6-12; EI ≥4); N=321

Intervention (8 weeks)
- Mesalamine delayed/slow release (0.5, 1.0, 1.5 g) three times daily

Dose Escalation in Patients Failing 5-ASAs: Kruis Study (2002)

• **Objective**
  – Compare balsalazide with mesalamine in mild-to-moderate UC

• **Design**
  – Multicenter, randomized, active-control, double-blind

• **Patients**
  – Active, mild-to-moderate UC (N=147)

• **Intervention (8 weeks)**
  – Balsalazide (2.25 g/d)
  – Balsalazide (6.75 g/d)
  – Mesalamine (2.4 g/d)

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Dose Escalation in Patients Failing 5-ASAs: Levine Study (2002)

For Most Measures, Tripling the Dose of Balsalazide did not Improve Efficacy

Improvement in Signs and Symptoms
After 8 Weeks of Treatment

Patients Improved

<table>
<thead>
<tr>
<th>Measure</th>
<th>BSZ 2.25</th>
<th>BSZ 6.75</th>
<th>Mesalamine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rectal Bleeding</td>
<td>p=0.045</td>
<td>p=0.013</td>
<td>p=0.032</td>
</tr>
<tr>
<td>Stool Frequency</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sigmoidoscopic Score</td>
<td></td>
<td></td>
<td>p=0.031</td>
</tr>
<tr>
<td>PGA</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Summary: Dose Escalation—What is the Evidence?

- Nearly 1/3 mesalamine non-responders
- Remission rates with Asacol 25% (Schroeder 1987), Lialda 40% (Kamm/Lichtenstein)
- Recent Ascend III is a non-inferiority trial: 4.8G not inferior to 2.4G
Nearly 1/3 mesalamine non-responders, may be able to salvage 50% by switching, combining or de-escalating.

- Safdi: Combination
- Lichtenstein: Low dose switch
Ulcerative Colitis is Not a Homogenous Disease

Disease Distribution of UC at Presentation

Goal of Therapy is to Deliver Active 5ASA to Site of Active Disease

- Different delivery strategies
- Delivery impacts dosing
5-ASA Delivery Systems

**Bacterial Cleavage**
- Sulfasalazine
- Olsalazine Dipentum™
- Balsalazide Colazal™

**pH Dependent Systems**
- Acrylic polymer coated mesalamine
  - Asacol™
  - Lialda™
- MMX™ mesalamine

**Time Release System**
- Ethylcellulose-encapsulated mesalamine microspheres
  - Pentasa™

**pH and Time Release System**
- Enteric coating; polymer matrix
  - Apriso™
## Oral 5-ASA Formulations: conjugated azo bond

<table>
<thead>
<tr>
<th>Agent (Trade Name)</th>
<th>Dosage Form</th>
<th>Delivery Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfasalazine (Azulfidine®; generics)</td>
<td>Tablet: 500 mg</td>
<td>Prodrug cleaved by colonic bacteria to 5-ASA and sulfapyridine (200 mg of 5-ASA)</td>
</tr>
<tr>
<td>Sulfasalazine (Azulfidine EN-Tabs®)</td>
<td>Delayed Release Tablet: 500 mg</td>
<td>Enteric coated to retard disintegration in stomach; prodrug cleaved by colonic bacteria to 5-ASA and sulfapyridine (200 mg of 5-ASA)</td>
</tr>
<tr>
<td>Osalazine (Dipentum®)</td>
<td>Capsule: 250 mg</td>
<td>Prodrug cleaved by colonic bacteria to 5-ASA (225 mg of 5-ASA)</td>
</tr>
<tr>
<td>Balsalazide (Colazal®)</td>
<td>Capsule: 750 mg</td>
<td>Prodrug cleaved by colonic bacteria to 5-ASA and 4-aminobenzoyl-β-alanine (262 mg of 5-ASA)</td>
</tr>
</tbody>
</table>

# Oral 5-ASA Formulations

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<th>Agent (Trade Name)</th>
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<tbody>
<tr>
<td>Mesalamine (Asacol®)</td>
<td>Delayed-release Tablet: 400 mg</td>
<td>Eudragit S coating dissolves at pH ≥7</td>
</tr>
<tr>
<td>Mesalamine (Lialda®)</td>
<td>Delayed-release Tablet: 1.2 g</td>
<td>Polymer film coating dissolves at pH ≥7 multi matrix system [MMX technology] prolongs dissolution in colon</td>
</tr>
<tr>
<td>Mesalamine (Pentasa®)</td>
<td>Controlled-release Capsule: 250 and 500 mg</td>
<td>Ethylcellulose coating microgranules provide time dependent release</td>
</tr>
<tr>
<td>Mesalamine (Apriso™)</td>
<td><strong>Delayed- and extended-release</strong> Capsule: 375 mg</td>
<td>Enteric coating dissolves at pH ≥6</td>
</tr>
</tbody>
</table>

## Dosing Considerations: Doses per Day

<table>
<thead>
<tr>
<th>Doses per day</th>
<th>Acute Dosing</th>
<th>Maintenance Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Once daily</td>
<td>Lialda® (mesalamine)</td>
<td>Apriso™ (mesalamine)</td>
</tr>
<tr>
<td>2X daily</td>
<td></td>
<td>Asacol® (mesalamine) Azulfidine® (sulfasalazine) Dipentum® (osalazine sodium)</td>
</tr>
<tr>
<td>3X daily</td>
<td>Asacol® (mesalamine)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Colazal® (basalazide disodium)</td>
<td></td>
</tr>
<tr>
<td>3X or 4X daily</td>
<td>Azulfidine® (sulfasalazine)</td>
<td></td>
</tr>
<tr>
<td>4X daily</td>
<td>Pentasa® (mesalamine)</td>
<td></td>
</tr>
</tbody>
</table>

## Dosing Considerations: Daily Tablet/Capsule Burden

<table>
<thead>
<tr>
<th>Daily Tablet/Capsule Burden</th>
<th>Acute Dosing</th>
<th>Maintenance Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 or 4</td>
<td>Lialda® (mesalamine)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>Apriso™ (mesalamine) Asacol® (mesalamine) Dipentum® (osalazine) Azulfidine® (sulfasalazine)</td>
</tr>
<tr>
<td>6</td>
<td>Asacol® (mesalamine)</td>
<td></td>
</tr>
<tr>
<td>6 or 8</td>
<td>Azulfidine® (sulfasalazine)</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Pentasa® (mesalamine)</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Colazal® (basalazide disodium)</td>
<td></td>
</tr>
</tbody>
</table>

Oral Versus Rectal Mesalamine Versus Combination Therapy in Active Distal Ulcerative Colitis

UC - Therapy of Active Disease

% Patients with cessation of bleeding

- Oral Mesalamine
- Rectal Mesalamine
- Combination

Week 1
Week 3
Week 6

*Safdi M et al. Amer J Gastroenterol 1997; 92:1867
Enema Formulations in Treating Acute Ulcerative Colitis

Distal UC - Therapy of Active Disease

Mesalazine Enemas as Maintenance Therapy in Ulcerative Colitis

Mesalamine Suppositories in the Treatment of Active Ulcerative Proctitis and Distal Ulcerative Colitis

Distal UC - Therapy of Active Disease

% Patients in Remission (4 weeks)

Placebo

Mesalamine suppository

Combination Therapy with Oral and Rectal Mesalamine for Maintaining Remission in Ulcerative Colitis

d'Albasio G et al. *Amer J Gastroenterol* 1997; 92:1143
Factors Affecting Adherence in UC

- **Patient-related factors**
  - Disease duration and extent
  - Single status
  - Male gender
  - Forgetfulness
  - Unable to see need for medication during remission

- **Economic**
  - Cost of filling Rx

- **Relationship with healthcare professional**
  - Lack of supportive relationship
  - Lack of adequate information/education

- **Medication-related factors**
  - Complicated dosing regimen
  - Fear of side effects
  - Impact of schedule on daily life
  - Large number of tablets

Kane SV. *Aliment Pharmacol Ther.* 2006;23(5):577-585.
Strategies for Improving Adherence

- Open communication between patients and providers
- Patient education regarding benefits of 5-ASA therapy
- Simplify dosing regimen
  - Individual therapy
  - Tailor regimen to patient’s lifestyle
- Minimize side effects
Nonadherence is common in patients with UC

- Up to 60% patients with quiescent UC are nonadherent with maintenance mesalamine
- Up to 60% of patients with UC take <70% of their prescribed medication

59/99 (60%) patients were nonadherent to maintenance 5-ASA therapy.

Patients Prefer QD Dosing

*Patients with UC in remission randomized to mesalamine granules 3 g QD (n=217), 1.5 g QD (n=212), or 0.5 g TID (n=218).
Improved Adherence With QD Mesalamine Dosing

UD = usual dosage (BID or TID).

Nonadherence Is Associated With Relapse in UC

Nearly 1/3 mesalamine non-responders. May be able to salvage 50% by switching, combining or de-escalating.

- Combination Strategies: Safdi /d’Albasio
- Low dose/ de-escalation switch: Lichtenstein
- Adherence strategies for long-term maintenance and chemoprevention warrant further studies: Importance of QD dosing