IBD: ASA dose, frequency, tailored delivery

Amer El-Sayed, MD
Rafik Hariri University Hospital
Founding Faculty, LAU-School of Medicine
LSGE, 8-9 October, 2010
5-Aminosalicylates (5-ASA)

- Benefit in IBD 1st described in 1942

![Diagram: SULFASALAZINE]

- Sulfapyridine (inactive carrier) linked to 5-ASA: Mesalamine (Therapeutic moiety)
- 5-ASA linked to sulfapyridine (anti-bacterial) by azo bond
- Sulfapyridine: carrier to deliver active drug to the colon (release by bacterial action)
5-Aminosalicylates (5-ASA)

- Partial small bowel absorption → 90% reach the colon
- Sulfapyridine: Hepatic acetylation → urinary excretion
- 5-ASA: acetylation by colonic epithelium
- 15%: D/C for side effects
- Intolerance to Sulfapyridine: side effects (90% will tolerate mesalamine)
5-ASA: Mechanism of action

- Not fully understood
- Inhibits cyclo-oxygenase and lipo-oxygenase pathways →↓ production of prostaglandins and leukotrienes (anti-inflammatory effect)
- PPAR γ activation
  - Peroxysome proliferator activation receptor gamma
  - Inhibits inflammatory response in several models of colitis (Katayama, Gastroenterology 2003)
  - Inhibits signal transduction and cell proliferation
- Reverse anti-proliferative effect of TNF-α →↓ intestinal cell transcription of inflammatory mediators
5-ASA: New formulations

- Key component in remission: amount of active drug reaching the site of inflammation
- Composed of 5-ASA only without carrier molecule
- Topical forms: direct delivery to rectum and colon
- Controlled release systems to allow targeted delivery of mesalamine to specific sites of the GI tract
5-ASA: 2 major delivery systems (1)- **Prodrug**

**Olsalazine (Dipentum®)**
- 5-ASA bound covalently to another 5-ASA
- Release by bacterial azo-reduction in the colon

**Balsalazide (Colazal®)**
- 5-ASA bonded to a benzoic acid derivative
- Both: pH independent
- Delivery: Colon
## 5-ASA: 2 major delivery systems (2)- 5-ASA coating

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Asacol®</th>
<th>Pentasa®</th>
<th>Salofalk®</th>
<th>MMX Lialda® mesalamine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preparation</td>
<td>400/800 mg tab, 500 mg supp, 4g/100 ml enema</td>
<td>500 mg tab, 1g sachets, 1g supp, 1g/100 ml enema</td>
<td>500 mg tab, 500 mg supp, 4g/60 ml enema</td>
<td>1.2 g tab</td>
</tr>
<tr>
<td>Coating</td>
<td>Eudragit-S</td>
<td>Ethylcellulose</td>
<td>Eudragit-L</td>
<td>Hydrophilic/lipophilic matrix</td>
</tr>
<tr>
<td>Solubility</td>
<td>pH ≥7</td>
<td>Continuous release- pH independent</td>
<td>pH≥6</td>
<td>pH &gt; 7 (TI)</td>
</tr>
<tr>
<td>Location of delivery</td>
<td>Terminal ileum, colon</td>
<td>Stomach to colon (75%)</td>
<td>Terminal ileum</td>
<td>Colon + rectum</td>
</tr>
</tbody>
</table>
# 5-ASA: side effects

<table>
<thead>
<tr>
<th>Common</th>
<th>rare</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>Pancreatitis, pericarditis</td>
</tr>
<tr>
<td>Vomiting</td>
<td>Hepatotoxicity</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>Drug-induced connective tissue disease</td>
</tr>
<tr>
<td>Anorexia</td>
<td>Bone marrow suppression</td>
</tr>
<tr>
<td>Headache</td>
<td>Hemolytic anemia</td>
</tr>
<tr>
<td>Hypersensitivity</td>
<td>Interstitial nephritis</td>
</tr>
</tbody>
</table>
5-ASA: poor adherence

- Poor adherence (<80% of prescribed dose)
  - 40% adherent
  - 100% relapsers at 1 yr were non-adherent
  - OR 5.5 (CI 2.3-13.2) for risk of relapse in poor adherence
- Low adherence:
  - Male gender
  - Single status
  - Full-time employment
  - Multiple concomittant drugs

Adherence in Patients Remaining in Remission

5-ASA: Failure to maximize mesalamine dose

- Variations in standard practice
- Katz and Pasquale (abstract, ACG 2009):
  - Dose of mesalamine before shifting to immunomodulator therapy
  - 39% patients were on 2.4g/d when shifted (despite current guidelines)
5-ASA: the solution: optimize drug delivery

• High dose / tablet formulations
• Once daily regimen (improves compliance)
• Novel formulations (more convenient dosing, improved drug delivery: MMX mesalamine)

• Explore the benefits of combination therapy
ACG GUIDELINES
ACG guidelines: mild/moderate distal U.C

INDUCTION

- **Topical mesalazine** superior to oral alone in achieving clinical improvement
  - Suppositories 500 mg BID or 1g/d
  - Enemas (1-4g) : 1g as affective as 4 g for induction in left-sided colitis
- **Oral therapy:**
  - Sulfasalazine: 4-6g/d QID
  - Mesalamine: 2.4 to 4.8 g/d (TID)
  - MMX: 2.4 to 4.8 g/d – 1 dose
- **Combination:** oral 2.4g/d + enema 4g/d >> either alone

MAINTENANCE

Topical

Suppositories:
- 500 mg QD or BID
- efficient- dose related relationship
- relapse at 1 yr: 10% if 500 mg BID, 36% if 500 mg QD

Enemas (2-4g)

<table>
<thead>
<tr>
<th>2-4 g enemas</th>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily</td>
<td>78%</td>
</tr>
<tr>
<td>Eod</td>
<td>72%</td>
</tr>
<tr>
<td>Etd</td>
<td>65%</td>
</tr>
</tbody>
</table>
ACG guidelines: mild/moderate distal U.C

**INDUCTION**

- **Topical mesalazine** superior to oral alone in achieving clinical improvement
  - Suppositories 500 mg BID or 1g/d
  - Enemas (1-4g): 1 g as effective as 4 g for induction in left-sided colitis
- **Oral therapy:**
  - Sulfasalazine: 4-6g/d QID
  - Mesalamine: 2.4 to 4.8 g/d (TID)
  - MMX: 2.4 to 4.8 g/d – 1 dose
- **Combination:** oral 2.4g/d + enema 4g/d >> either alone

**MAINTENANCE**

**Oral therapy:**
- Sulfasalazine: 2g/d
- Eudragit-S Mesalamine: 3.2 g/d
- Extended release granules: 1.5 g/d

**Combination**
- oral 1.6 g/d + enema 4g twice weekly superior to oral alone

(d’Albazio et al, Am J Gastro 1997)
**ACG guidelines: extensive, mild to moderate disease**

**INDUCTION**

- Newer 5-ASA molecules (Asacol®, Pentasa®, Dipentum®, Colazal®, MMX)
  - All superior to placebo, as effective as sulfasalazine in acute treatment
- Therapeutic benefit requires threshold dose (< 2g/d ineffective)
- 2 dose-ranging studies: ASCEND I & II
- Combination: oral + topical superior to oral alone in clinical remission at 8 weeks  
  (Marteau et al, Gut 2005)
ACG guidelines: extensive, mild to moderate disease

MAINTENANCE

• Newer 5-ASA molecules shown to reduce relapse rates
• Increased efficacy with higher doses up to 4.8g/d of mesalamine
5-ASA dose: The evidence (ASCEND TRIALS)
Dose-response effect of 5-ASA in induction/remission of UC
• Definition:
  – Mild disease: < 4 BM/day, minimal rectal bleeding, no abdominal pain or urgency
  – Moderate disease: 4-6 BM/day, urgency, tenesmus

• Question: is the initial dose 4.8 g/day delayed release mesalamine Asacol® (800 mg tabs) more effective than 2.4 g/day (400 mg tabs) in mild/moderate UC?

• Dose-response effect?
ASCEND I TRIAL
Hanauer et al., Can J Gastroenterol 2007

- 301 patients with mild/moderate UC
- 2.4 g/d (400 mg) vs. 4.8 g/d (800 mg) day delayed release oral mesalamine (Asacol®)
- Primary endpoint: overall improvement at week 6
  - Complete remission
  - Response to therapy
ASCEND I TRIAL
Hanauer et al., 2007

• OVERALL POPULATION
  • Equivalent efficacy: No significant difference between 2.4 g and 4.8 g/day (p=0.441)

• SUBGROUP ANALYSIS (moderate disease)
  • higher efficacy with high dose mesalamine (p=0.03)

CONCLUSION:
- Asacol® effective in mild/moderate disease
- Greater benefit of higher dose in moderate disease
ASCEND II TRIAL
Hanauer et al., Am J Gastroenterol 2005

- 386 patients with moderate UC only
- Double blind, RCT to evaluate the efficacy of 4.8 g/d delayed release oral mesalamine
- 2.4 g/d (400 mg tabs) vs. 4.8 g/day (800 mg tabs) Asacol® for 6 weeks
- Primary endpoint: overall improvement at week 6
  - Complete remission
  - Response to therapy
ASCEND II TRIAL  
Hanauer et al., 2005

Treatment success:
59% (2.4g/d) vs. 72% (4.8g/d)  
P = 0.038

CONCLUSION:
Patients with moderate U.C more likely to achieve treatment success with higher dose
Median time to resolution of symptoms

- Faster resolution of symptoms (combined rectal bleed and stool frequency)
- Faster resolution in patients previously treated with 2 or more therapies (25d vs. 49d, p<0.05)

CONCLUSION: MAGNITUDE OF DOSE BENEFIT OF 4.8 g/d greater in difficult to treat patients
ASCEND III TRIAL
Sandborn et al., Gastroenterology 2009

• 772 patients with moderate UC only
• Double blind, RCT to evaluate the non-inferiority of 4.8 g/d delayed release oral mesalamine
• 2.4 g/d (400 mg tabs) vs. 4.8 g/day (800 mg tabs) Asacol® for 6 weeks
• Primary endpoint: overall improvement
  – Improvement in physician global assessment (rectal bleed, stool frequency, sigmoidoscopy)
ASCEND III TRIAL
Sandborn et al., Gastroenterology 2009

Non-inferiority of 4.8 g/d in overall improvement

Treatment success (overall improvement)
95% CI (-11.2, 1.9)

Clinical remission
SUBGROUP ANALYSIS

Greater benefit of higher dose in difficult to treat patients:
- Previous therapy with corticosteroids, oral 5-ASA, topical therapies
- Patients with multiple medications simultaneously
ASCEND I,II,III CONCLUSIONS

- High dose equivalent to low dose in mild disease
- Greater benefit in moderate disease and difficult to treat patients
- Long-term benefits:
  - Avoidance of toxic/costly drugs
  - Improved quality of life
  - Decrease need for colectomy
  - Decreased risk of CRC
5-ASA frequency: once daily vs. multiple dosing
QDIEM study: once daily vs. twice daily Asacol® in maintenance

- 1,023 patients with ulcerative colitis
- Doses 1.6 g/d to 2.4g/d randomized to QD or BID for 6 months (400 mg tabs)
- Primary EP: % of patients remaining in remission

<table>
<thead>
<tr>
<th></th>
<th>Once daily</th>
<th>Twice daily</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remission at 6 mo</td>
<td>90.5%</td>
<td>91.8%</td>
</tr>
</tbody>
</table>

- Once daily as effective, equivalent safety profile and relapse rates

Novel formulation: MMX Mesalamine

- High strength 1.2 g mesalamine formulation
- MMX technology: combines pH-dependent gastro-resistant film (delayed initial release to terminal ileum)
  - Hydrophilic and lipophilic matrices that turn into gel mass when in contact with intestinal fluid
- Homogeneous distribution throughout the colon
MMX for induction in mild to moderate UC
Lichtenstein et al., Clin Gastroenterol Hepatol 2007

- MMX 2.4g/d (BID) vs. MMX 4.8g/d (once daily) vs. placebo (n=280)
- Primary endpoint: remission
  - UCDAI ≤ 1
  - Rectal bleeding/stool frequency scores = 0
  - ≥ 1 point decrease in sigmoidoscopy score
Significant advantage of MMX in BID and once daily doses over placebo

MMX 2.4 vs. MMX 4.8 vs. placebo
Lichtenstein et al., Clin Gastroenterol Hepatol 2007
MMX vs. Asacol® vs. placebo (mild to moderate UC)

- MMX 2.4g QD vs. MMX 4.8g QD vs. Asacol® 2.4 g (800mg TID) vs. placebo (n=343)
- Significant advantage of MMX over placebo for overall remission
- Advantage of MMX and Asacol vs. placebo in clinical improvement and endoscopic score (p < 0.03)

BOTH INDUCTION STUDIES:
- MMX 4.8 superior to 2.4 in endoscopic score: consistent with higher mucosal levels
- Once daily convenient and efficient
MMX in maintenance
Prantera et al., Gastroenterology 2008

- Placebo-controlled trial (n=381)
- MMX 2.4 g once daily vs. Asacol® 2.4 g (twice)

<table>
<thead>
<tr>
<th></th>
<th>Clinical remission (12 months)</th>
<th>Clinical + Endoscopic remission (12 mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMX 2.4 g (QD)</td>
<td>68%</td>
<td>60.9%</td>
</tr>
<tr>
<td>Asacol 2.4g (BID)</td>
<td>65.9%</td>
<td>61.7%</td>
</tr>
</tbody>
</table>
Benefit of combination therapy. Extensive moderate disease.
Marteau et al, Gut 2005

- Double blind, RCT (n=127)
- Combination oral Pentasa® 4g/d + 1g enema vs. placebo
- Significant advantage for combination therapy in terms of clinical improvement
- Faster induction, resolution of symptoms
5-ASA and colorectal cancer

- Pooled Odds ratio for protective association between 5-ASA and CRC:
  OR 0.51 (95% CI: 0.37-0.69)
- Odds ratio for combined endpoints CRC and dysplasia
  OR 0.5 (95% CI 0.38-0.69)

CONCLUSION

• 5-ASA: foundation for treatment of IBD, esp. U.C for induction and maintenance in mild/moderate disease
• Efficacy dose-dependent
  – 4.8g/d → optimal for induction
  – 2.4 g/d → optimal for maintenance
• Overall Rx decisions based on severity and extent
• Use most appropriate delivery formulation according to area involved
• Compliance: restrictive factor. Use newer formulations for once daily dosing