Evidence-based Medicine: Treatment of Ulcerative Colitis

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Sulfasalazine

Aminosalycilates: 6 oral and 2 topical preparation [enema and suppository].

Budesonide: 1 oral and one topical preparation [foam]).

Steroids: oral and 2 topical preparations [enema and foam].

Immunomodulator/ Immunosuppressants: thiopurines (azathioprine, 6-mercaptopurine), cyclosporine, tacrolimus.

Anti-TNF agents : infliximab, adalimumab, golimumab.

Anti-adhesion agents: vedolizumab.

Surgery
Ulcerative Colitis – Clinical Care Pathway

Stratify according to colectomy risk

Low Risk Patient

- Mild-moderate disease activity
  - <6 bloody bowel movements
  - No systemic signs of toxicity
- Limited anatomic extent
- Mild endoscopic activity

High Risk Patient

- Severe disease activity
  - ≥6 bloody bowel movement/day
  - and
  - Fever >99.5 F or
  - Tachycardia >90 BPM
  - Hemoglobin <10.5 mg/dl or
  - ESR > 30 mm or CRP > 30 mg/l
- Deep ulcer on endoscopy
- Extensive colitis
- C. diff or CMV infection
- Steroid requiring disease

adapted from Dassopoulos 2014
Algorithm for Induction and Maintenance of Remission in Mild-Moderate, Low-Risk Ulcerative Colitis

Low Risk Flare with mild to moderate activity
5-ASA +/- local therapy or Budesonide MMX

[Pathway: Remission → Oral steroids or Budesonide MMX
 +/- oral 5-ASA]

[If no Remission: Recurrence after steroid induction; Steroid dependent/ refractory course
High risk outpatient Induction and Maintenance Therapy]

Maintenance therapy 5-ASA

Adapted from Dassopoulos 2014 and Bressler et al. 2015
## Approved 5-Aminosalycilates

<table>
<thead>
<tr>
<th>Rectal Preparations</th>
<th>Azo-bonded Pro-drug</th>
<th>Moisture Dependent</th>
<th>Delayed Release pH ≥7</th>
<th>Delayed + Extended Release pH ≥6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rowasa® (mesalamine)</td>
<td>Azulfidine® (sulfasalazine)</td>
<td>Pentasa® (mesalamine)</td>
<td>Asacol® (mesalamine)</td>
<td>APRISO™ (mesalamine)</td>
</tr>
<tr>
<td>Canasa® (mesalamine)</td>
<td>Dipentum® (olsalazine)</td>
<td></td>
<td>Lialda® (mesalamine)</td>
<td></td>
</tr>
<tr>
<td>Colazal® (balsalazide disodium)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **Rectum / left-colon**
- **Colon**
- **Small bowel / right colon**
- **Terminal ileum / colon**
- **Terminal ileum / colon**
5-Aminosalycilates for Induction of Remission in Mild-Moderate UC

- All 5-aminosalycilates are similar in clinical efficacy
- Efficacy for induction of response is 50%-70%
- Efficacy for induction of remission is 15%-40%
- Higher efficacy by combining oral and topical (enema) 5-ASA formulations in left-sided and pan-colitis
- Overall excellent safety profile
- Similar adverse events except
  - Sulfasalazine (sulfa allergy)
  - Looser stools often seen with olsalazine

**Differences**
- Pill burden and dosing frequency
  - may or may not influence adherence
- Insurance coverage

Colonic distribution of sulfasalazine enemas 100 ml

Left sided colitis, Moderate active

10 min after application and positioning in left lateral position

## Local therapy of left sided ulcerative colitis -Metaanalysis-

<table>
<thead>
<tr>
<th>Active disease</th>
<th>Pooled Odds ratio (95% CI)</th>
<th>Trials n</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Clinical remission</td>
<td>Clinical improvement</td>
</tr>
<tr>
<td>Rectal 5-ASA vs. placebo</td>
<td>7.7 (4.8-12.3)</td>
<td>6.9 (4.8-9.8)</td>
</tr>
<tr>
<td>Rectal 5-ASA vs. rectal steroids</td>
<td>2.4 (1.7-3.4)</td>
<td>1.4 (0.9-2.1)</td>
</tr>
<tr>
<td>Rectal vs. oral 5-ASA</td>
<td>4.1 (1.5-10.9)</td>
<td>6.3 (2.7-14.5)</td>
</tr>
</tbody>
</table>

Oral versus Rectal Mesalamine versus Combination Therapy in the Treatment of Distal Ulcerative Colitis

Improvement disease activity index (DAI)

- 5-ASA oral 3x800mg/d
- 5-ASA 4g/d enema
- Combination

n=60

3 weeks: 2.9, 3.8, 3.9
6 weeks: 3.9, 4.4, 5.2

*p<0.05 vs. oral 5-ASA

4.8 g Mesalamine/day is Not Superior to 2.4 g/d Mesalamine in Mild-Moderate UC

A; Ascend II and Ascend III

Budesonide MMX for Mild-Moderate Ulcerative Colitis Remission at Week 8

Patients in remission: combined clinical and endoscopic remission

- Placebo: 7%
- MMX 9 mg: 18%
- MMX 6 mg: 13%
- 5-ASA 2.4 g: 12%

p<0.01

p<NS

High risk Flare with moderate-severe activity
Oral steroids +/- oral 5-ASA

Maintenance therapy 5-ASA

Discuss Colectomy and IPAA

Steroid refractory, no response to initial therapy and worsening clinical symptoms

Severe activity or Recurrence after steroid induction; Steroid dependent/refractory course

Steroid responsive:
• Thiopurine monotherapy

Steroid responsive or refractory:
• Anti-TNF therapy (infliximab, adalimumab, golimumab) +/- thiopurine [or methotrexate]
• Vedolizumab +/- thiopurine or methotrexate

adapted from Dassopoulos 2014 and Bressler et al. 2015
Maintenance of Remission in Ulcerative Colitis by Azathioprine or 6-MP

Comparative Efficacy of Biologics for Moderately to Severely Active Ulcerative Colitis.


Systematic Review with Network Meta-Analysis
Steroid-free Remission

Response

Mucosal Healing

Patients naïve to anti-TNF and AZA or >3 months stop of AZA before trial

Remission: Steroid-free + Mayo <2, Mucosal Healing: endoscopy 0 or 1
## Comparative Effectiveness Trails of Anti-TNF Agents in Ulcerative Colitis

<table>
<thead>
<tr>
<th></th>
<th>Infliximab</th>
<th>Golimumab</th>
<th>Adalimumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infliximab</td>
<td></td>
<td>214 / 1870</td>
<td>174 / 204</td>
</tr>
<tr>
<td>Golimumab</td>
<td>214 / 1870</td>
<td></td>
<td>13562 / 420</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>174 / 204</td>
<td>13562 / 420</td>
<td></td>
</tr>
</tbody>
</table>

Total number of subjects required for comparative efficacy RCTs between anti-TNF agents for *Induction / Maintenance* of remission.

Infliximab Concentration and Clinical Outcome – ACT1 and ACT2 Study

Infliximab 5 mg/kg bodyweight week 0,2,6, IFX level week 8

Proportion of Patients in Remission (%)

<table>
<thead>
<tr>
<th>Quartile</th>
<th>Week 8</th>
<th>Week 30</th>
<th>Week 54</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st</td>
<td>26.3</td>
<td>14.6</td>
<td>21.1</td>
</tr>
<tr>
<td>2nd</td>
<td>≥21.3- &lt;33.0</td>
<td>≥2.4- &lt;6.8</td>
<td>≥1.4- &lt;3.6</td>
</tr>
<tr>
<td>3rd</td>
<td>≥33.0- &lt;47.9</td>
<td>≥3.6- &lt;8.1</td>
<td>&gt;8.1</td>
</tr>
<tr>
<td>4th</td>
<td>&gt;47.9</td>
<td>&gt;6.8</td>
<td>60.0</td>
</tr>
</tbody>
</table>

Week 8: p = 0.05
Week 30: p = 0.0001
Week 54: p = 0.007

### Vedolizumab (VDZ) in UC – Clinical Response and Remission Week 6 Depending on Prior anti-TNF Exposure

<table>
<thead>
<tr>
<th>Prior anti-TNF</th>
<th>Clinical Response</th>
<th>Clinical Remission</th>
<th>Clinical Response</th>
<th>Clinical Remission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>20.6%</td>
<td>3.2%</td>
<td>26.3%</td>
<td>6.6%</td>
</tr>
<tr>
<td>VDZ</td>
<td>39.0%</td>
<td>9.8%</td>
<td>53.1%</td>
<td>23.1%</td>
</tr>
</tbody>
</table>

*Delta: 18.4%, Delta: 6.6%, Delta: 26.8%, Delta: 16.5%*

**n=206, n=145**

Algorithm for Maintenance of Remission in Moderate-Severe, High-Risk Ulcerative Colitis (Outpatient)

**Failure to maintain remission on thiopurines or vedolizumab**

**Thiopurines**
- Check 6-TGN levels
  - **6-TGN < 230**
    - Increase thiopurine dose
  - **6-TGN > 230**
    - Switch drug class
- **6-TGN < 230, 6-MMP high**
  - Consider adding allopurinol + reduce thiopurine dose to 20-25% of previous dose

**Vedolizumab**
- Increase dose to 300 mg / q 4 weeks
- [Consider adding immunomodulator]

**Course of disease, risk factors for CRC**
- Discuss Colectomy and IPAA

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adapted from Dassopoulos 2014 and Bressler et al. 2015
Algorithm for Maintenance of Remission in Moderate-Severe, High-Risk Ulcerative Colitis (Outpatient)

Failure to maintain remission on anti-TNF

- Low level, no antibody
  - Increase dose
  - If no response switch to another anti-TNF or out of class

- Low level, high antibodies
  - Switch class
  - or increase dose + add immunomodulators

- Therapeutic level
  - Switch class

Check anti-TNF levels + drug antibodies

adapted from Dassopoulos 2014 and Bressler et al. 2015
Things should be made as simple as possible but not any simpler

Albert Einstein
Conventional Treatment Strategy for Ulcerative Colitis

- Aminosalicylate
- Corticosteroid
- Anti-TNF
  - Vedolizumab
  - Cyclosporine
- Anti-TNF
  - Vedolizumab
  - Thiopurine
- Surgery

- Aminosalicylate or
  - Thiopurine or
  - Vedolizumab

- Induction
- Maintenance

Step-Up according to severity or failure at prior step

adapted from S. Hanauer