Mild-moderate Ulcerative Colitis
Sequential & Combined treatments need to be tested

Philippe Marteau, Paris, France
Sequential vs combined treatments

When should one switch?
Sequential vs combined treatments

When should one switch?
When the statistician says it is optimal to do it?
This should be based on studies…
When the patient asks for it?
Sequential vs combined treatments

Switch or combine?  
When?  
What?
Combination therapy recommended

...Topical steroids or mesalazine alone are also effective, but less effective than combination therapy [EL1b, RG B].

Topical 5-ASA is more effective than topical steroid [EL1a, RG A].

Oral aminosalicylates alone are less effective [EL1a, RG A].

Systemic corticosteroids are appropriate if symptoms of active colitis do not respond rapidly to mesalazine [EL1b, RG C].

Travis et al. JCC 2008
Extensive ulcerative colitis of mild-moderate severity should initially be treated with mesalazine \( \geq 2 \text{g/day} \) [EL1a, RG A], combined with topical mesalazine [EL1b, RG A]. “combined treatment”

Oral aminosalicylates alone induce remission only in a minority of patients [EL1a, RG A]

Systemic corticosteroids are appropriate
- if symptoms of colitis do not respond rapidly to mesalazine [EL1b, RG C],
- or in pts who are already taking appropriate maintenance therapy

Travis et al. JCC 2008
Oral 5-ASA vs rectal (enema) vs combined for active distal UC

Fig. 2. Individual DAI scale of rectal bleeding; percent of patients reporting no blood in stools (DAI responses classified as “no blood, blood, or missing”). *p < 0.05 versus Asacol.

Combined oral and enema treatment with Pentasa (mesalazine) is superior to oral therapy alone in patients with extensive mild/moderate active ulcerative colitis: a randomised, double blind, placebo controlled study


5-ASA orally + pentasa enema
5-ASA orally + placebo enema

Combined

Marteau et al. 2005
The time to cessation of rectal bleeding was significantly shorter for patients under treatment with the combined treatment ($p=0.0031$)

Marteau et al. 2005
Combined treatment is as well tolerated

- **Acceptability of combination therapy**
  84% of the combined, and 85% of the placebo enema group willing to take a combination therapy in the future

AEs NS

*Probert C et al. BSG March 2005*

14 patients No difference in créatinine, proteinuria, urine hemoglobin renal excretion of 5-ASA, acetyl 5-ASA

*Probert et al. 2006*
Combination of topical steroids and salicylates in distal UC

double blind RCT n = 60
3mg beclométasone enemas or 1g 5-ASA enema or association

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<tr>
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<th>Béclom.</th>
<th>5-ASA</th>
<th>Combined</th>
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<tbody>
<tr>
<td>Clinical improvement</td>
<td>70 %</td>
<td>76 %</td>
<td>100 %</td>
</tr>
<tr>
<td>Endoscopy improvement</td>
<td>75 %</td>
<td>71 %</td>
<td>100 %</td>
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<tr>
<td>Endoscopic remission</td>
<td>30 %</td>
<td>10 %</td>
<td>37 %</td>
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✔️ superiority of the combined treatment

Pts with persistently active, steroid-refractory disease should be treated with azathioprine/mercaptopurine [EL1b, RG B]

although surgical options should also be considered and discussed,

Intravenous steroids, infliximab [EL1b, RG B] or calcineurin inhibitors [EL3, RG C] should also be considered.

Travis et al. JCC 2008
ECCO Statement: Thiopurine-intolerant or -refractory UC

- **Infliximab** [EL1b, RG B] or surgical options should be considered.
- Continued medical therapy that does not achieve steroid-free remission is not recommended [EL5, RG D].

Travis et al. JCC 2008
Combined treatments with 5-ASA?

5-ASA +
- Salicylates
- Steroids
- Purine analogs
- Infliximab

- More effective?
  - Inflammation?
  - Cancer prevention?
- Tolerance?
- Interaction?
  - additivity?
  - synergism-potentiation?
Purine analogs

Variations
Genetically determined
High activity: 89%
Intermediate: 11%
Very low: 0.3%

Drug interference? adaptation?

Azathioprine

6-MP

TPMT

inactive metabolites
active 6-TGN

X.O.

HGPRT
In vitro inhibition of TMPT by aminosalicylates


IC50 of TPMT (Inhib. Conc. 50% - μmol/L)
Olsalazine: 23
Sulfasalazine: 70
N-ac-5ASA: 390
5-ASA: 1240
In vivo interaction in between purine analogs and 5-ASA?

- Lowry et al. Gut 2001

Open 34 Crohn - Aza or 6-MP + 8 weeks
5-ASA 4g/j Sulfasalazine 4 g/j or Balasalazide 6.75 g/j
Facts: Combined treatments with 5-ASA are
  • well tolerated (also with purine analogs)
  • steroid sparing (dose)
  • more effective (for distal and for extensive UC)

Questions & ideas:
  • maintenance of 5-ASA for cancer prevention
  • mucosal healing
  • other associations?

Combined treatments need to be more tested in real life and clinical trials