Features of Drugs Used in IBD: 5-Aminosalicylic Acid

U. Klotz (Stuttgart)

- Target and local availability of 5-ASA (topical action)
- Clinical use of 5-ASA
- Disposition (PK properties) of 5-ASA
- Are there “therapeutic” target levels?
- Safety profile of 5-ASA
- Mode of action of 5-ASA
- Chemoprevention of colorectal cancer by 5-ASA
- Conclusions
Factors Involved in IBD

- oxygen radicals / NO
- luminal antigens and microflora
- disturbed immune response
- IL-1β/4/12/13/18; TNF-α; IFN-γ
- local ischemia

- antioxidants
- defensins
- innate / acquired immunity
- IL-10; TGF-β1; EGF

- protective factors
  (anti-inflammatory)

- damaging factors
  (inflammatory stimuli)

- balanced mucosal barrier

- genetic variability
  (e.g. receptors, second messengers, transporters)
Rational for Development of Intestinal Drug Delivery Systems of 5-ASA

Target: inflamed (sub)mucosa of small and/or large bowel

Drug delivery: by oral and/or rectal route for topical action

Local availability: sufficient intraluminal concentrations uptake in intestinal mucosa and inflammatory cells

Limited systemic drug exposure: safety aspects
# Place of 5-ASA in the Management of IBD

<table>
<thead>
<tr>
<th>Ulcerative Colitis (UC)</th>
<th>Crohn’s Disease (CD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>first choice in mild to moderate active UC</td>
<td>benefit of 5-ASA is limited in active CD</td>
</tr>
<tr>
<td>if remission has been achieved medically, maintenance with 5-ASA should be preferred</td>
<td>if remission has been achieved medically, maintenance with 5-ASA is a treatment option</td>
</tr>
<tr>
<td>for patients in remission on 5-ASA treatment should be extended at least for one year</td>
<td>for patients in remission on 5-ASA cessation of treatment may be considered after 2 years of full remission</td>
</tr>
<tr>
<td>5-ASA can reduce risk for colon cancer</td>
<td></td>
</tr>
</tbody>
</table>

according to guidelines of the IBD section of the Br. Soc. Gastroenterol. published in GUT 53 (Suppl 5) v1-16 (2004)
Ulcerative Colitis (UC)

- 90% of all cases are mild or moderate in severity

- at least 2/3 have endoscopic involvement distal to splenic flexure

rectal (topical) therapy with 5-ASA

Suppositories  proctitis and distal sigmoiditis

Enemas, foam  proctosigmoiditis, left-sided colitis
(gel)  combined (rectal + oral) treatment

(P. Gionchetti et al., 2006)
Disposition of 5-ASA

30 – 55% of D (feces)
Intraluminal concentrations of 5-ASA in the colon (2g/day):
10 – 25 mmol/l (Laursen et al., 1990)
## Pharmacokinetic Properties of 5-ASA in Man

<table>
<thead>
<tr>
<th>Parameter (ranges)</th>
<th>5-ASA</th>
<th>Ac-5-ASA</th>
</tr>
</thead>
<tbody>
<tr>
<td>$t_{1/2}$ [h]</td>
<td>0.5 – 2.4 *</td>
<td>1.3 - 11</td>
</tr>
<tr>
<td>CL [ml/min]</td>
<td>300 – 690 *</td>
<td>200 – 300 (renal CL)</td>
</tr>
<tr>
<td>dialysance [ml/min]</td>
<td>-</td>
<td>60 - 100</td>
</tr>
<tr>
<td>protein binding [%]</td>
<td>43</td>
<td>78</td>
</tr>
<tr>
<td>V [l/kg]</td>
<td>0.3 – 0.5</td>
<td>-</td>
</tr>
<tr>
<td>renal excretion [% of dose]</td>
<td>6 – 13</td>
<td>24 - 41</td>
</tr>
<tr>
<td>faecal excretion [% of dose]</td>
<td>13 – 28</td>
<td>15 - 25</td>
</tr>
<tr>
<td>biliary excretion [% of dose]</td>
<td></td>
<td>0.01 – 0.75 (total 5-ASA)</td>
</tr>
<tr>
<td>excretion into breast milk</td>
<td>0.01 – 0.02</td>
<td>1.5 – 3.6</td>
</tr>
<tr>
<td>[mg in 120 – 200 ml]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* dose dependent
"Therapeutic" Target Levels of 5-ASA

25 post-operative patients with Crohn’s disease (colon-ileoscopy) mucosal levels at perianastomotic area during oral treatment with 2.4 g 5-ASA/day

- < 20 ng/mg
- > 100 ng/mg

endoscopic recurrence at the neo-ileal site in 10 patients (mean time from surgery 14 month)

- no recurrences

21 patients with active (mild to moderate) ulcerative colitis mucosal 5-ASA concentrations in rectum biopsies during oral treatment with 2.4 to 3.2 g 5-ASA/day:

- endoscopic scores
  - 0 - 1: 16.1 ng/mg (10.2 - 45) p < 0.03
  - 2 - 3: 5.5 ng/mg (3.5 - 17.4)

- histol. inflamm. score
  - low: 17.4 ng/mg (10.5 - 45) p < 0.01
  - severe: 8.9 ng/mg (3.5 - 17.2)

(G. Frieri et al., 2000)
Correlation between mucosal concentrations of 5-aminosalicylic acid (5-ASA) and soluble interleukin 2 receptor (sIL-2R) as biomarker of inflammation

(G.Frieri et al., 2000)
# Plasma and Mucosal Levels in Patients with UC

*(G.D’Haens et al., 2006)*

<table>
<thead>
<tr>
<th>at week 8 of treatment with oral MMX-5-ASA</th>
<th>1.2 mg (n = 13/7)</th>
<th>2.4 mg (n = 14/11)</th>
<th>4.8 mg (n = 11/10)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>geometr. mean in plasma</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-ASA [ng/ml]</td>
<td>284</td>
<td>511</td>
<td>1926</td>
</tr>
<tr>
<td>Ac-5-ASA</td>
<td>783</td>
<td>1514</td>
<td>2865</td>
</tr>
<tr>
<td><strong>mucosal levels</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-ASA [ng/ml]</td>
<td>11</td>
<td>7</td>
<td>49</td>
</tr>
<tr>
<td>Ac-5-ASA</td>
<td>9</td>
<td>7</td>
<td>30</td>
</tr>
<tr>
<td><strong>remission rate [%]</strong></td>
<td>0</td>
<td>31</td>
<td>18</td>
</tr>
<tr>
<td>UC-DAI [improvement]</td>
<td>1.0</td>
<td>3.3</td>
<td>5.7</td>
</tr>
<tr>
<td>histol. score [improvement]</td>
<td>-1 to 1</td>
<td>0.5 to 3.0</td>
<td>3.0 to 4.5</td>
</tr>
<tr>
<td><strong>AE related to treatment</strong></td>
<td>3</td>
<td>5</td>
<td>2</td>
</tr>
</tbody>
</table>

(Headache most frequent)

UK2708
Tissue Mesalazine Concentrations

G. Frieri et al. (1999)

Distribution of mesalazine mucosal concentrations in the rectum and descending colon in patients on oral (2.4g/day; n = 11) and oral plus topical (4g/day 100ml enema; n = 9) treatment.
Combined Oral & Enema Treatment with 5-ASA  
*(P. Marteau et al., 2005)*

<table>
<thead>
<tr>
<th>Clinical outcome (mean ± 95% CI; ITT)</th>
<th>patients with extensive mild/moderate active UC po: 2 x 2g 5-ASA/day for 8 weeks + 1 g enema (bedtime; n = 58) + placebo (n = 47)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remission 4 weeks</td>
<td>44% (31 – 58%)</td>
</tr>
</tbody>
</table>
| Rates 8 weeks                        | 64% (50 – 76%)  
P = 0.03                                                                                                       |
| Clinical 4 weeks                     | 89% (78 – 96%)  
P = 0.001                                                                                                      |
| Improvement 8 weeks                  | 86% (75 – 94%)  
P = 0.026                                                                                                      |
|                                      | 68% (53 – 81%)                                                                                                                  |
Risks for Nephrotoxicity in IBD

U.K. General Practice Research Database

Incidence rates/100 patients & year:

- Patients without IBD: 0.08
- IBD-patients without 5-ASA: 0.25
- IBD-patients on 5-ASA: 0.17
- Patients with act. RA on SZ: 0.29

(T.P. van Staa et al., 2004)

Postal questionnaire to 1298 British gastroenterologists and 290 consultants of the Renal Association to report cases of 5-ASA-induced impairment in kidney function: retrospective estimation (based on IBD prevalence and treatment in UK) approx. 1 case in 4000 patients/year

(A.F. Müller et al., 2005)

153 outpatients with CD (mean exposure to 9 kg of 5-ASA within 8.6 years): CL creat ↓ 0.3 ml/min per year corresponds to expected age-related decline

(D.J. deJong et al., 2005)
Mode of Action of Polypotent 5-ASA

- production of proinflammatory PG/LT↓
- impairing production/release of TNF-α, interleukin 1 and 8
- inhibiting chemotaxis and adhesion of inflammatory cells
- inducing changes in apoptosis, proliferation or epithelial wound healing
- scavenging free (toxic) oxygen radicals
- inhibiting activation of NF-kB
- activating peroxisome proliferator-activated receptors (PPAR-γ)

(P. Descreumaux & S. Ghosh, 2006)
New Indications for 5-ASA

in patients with UC chemoprevention of colorectal cancer by
≥ 1.2/day of 5-ASA (risk reduction by 50 up to 75 %)

**OR = 0.51** (0.37 – 0.69) based on 9 studies (F.S. Velayos et al., 2005)

COX dependent (reversible inhibition of COX-1/2; IC$_{50}$: 0.2 – 1mM)

independent mechanisms; e.g.:

- inhibition of cell proliferation
- activation of apoptotic processes
- inhibition of NF-κB activation (MRP kinases Bcl-2; IC$_{50}$: 2 – 20mM)
- inhibition of DNA-hydroxylation (IC$_{90}$: 5mM) which impairs DNA repair
- scavenging toxic (DNA-damaging) free radicals (0.3 mM)
- Increasing maintenance of genomic stability (10 – 40 mM)

(T.P. van Staa et al., 2005; E.F. Stange, 2006; P. Meinkholm et al., 2006
M. G. Luciani et al., 2007)

UK 2295
Conclusions

1. 5-ASA – drug of first choice in UC (CD)

2. Topical targeting important (e.g. ointment/spray for oral CD)
   
   K. Otake et al., 2007

1. PK, mode of action and safety well documented

2. New indication (novel compounds with dual action?)