Crohn's disease
Appendix L

Clinical Guideline <...>
5-ASA adverse-event data
10 October 2012

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1 Observational data on adverse events associated with 5-ASA treatment

Risks of particular concern to the GDG which are associated with 5-ASA treatments include:
- acute pancreatitis (1% in adults)
- renal dysfunction (less than 1%). However, routine monitoring of renal function is advised in the BNF.

Incidence rates of 5-ASA adverse event data were collected and are presented in tabular format.

The 5-ASA safety review included the following serious adverse events:
- Interstitial nephritis
- Pancreatitis
- Hepatitis
- Pericarditis
- Pulmonary toxicity
- Blood Dyscrasias
- Neonatal cerebral vein thrombosis (CVT) in mothers taking 5-ASA
- Any other reported serious adverse event
### 5-ASA safety data: serious adverse events in people with Crohn’s disease

<table>
<thead>
<tr>
<th>Study type, reference, country</th>
<th>Drug</th>
<th>No with Crohn’s disease</th>
<th>Total number</th>
<th>Follow up</th>
<th>Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pure CD population</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Singleton et al, 1993&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Mesalazine</td>
<td>310</td>
<td>310 CD patients (230 treated with mesalazine)</td>
<td>16 weeks treatment</td>
<td>No serious adverse events were reported in either group, but note that only events occurring in &gt; 1% of patients are recorded</td>
</tr>
<tr>
<td>Denmark Multicentre RCT</td>
<td>Mesalazine</td>
<td>293</td>
<td>293 patients with Crohn’s disease (CD; 141 taking mesalazine)</td>
<td>48 weeks treatment</td>
<td>1/141 (0.7%) with pancreatitis (that caused withdrawal)</td>
</tr>
<tr>
<td>Sutherland et al, 1997&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Mesalazine</td>
<td>163</td>
<td>163 CD patients (87 in treatment group)</td>
<td>72 months treatment</td>
<td>1/87 (1.1%) pancreatitis</td>
</tr>
<tr>
<td>McLeod et al, 1995&lt;sup&gt;3&lt;/sup&gt;</td>
<td>Mesalazine</td>
<td>78</td>
<td>78 CD patients (37 treated with mesalazine)</td>
<td>12 months</td>
<td>0/37 (0%) pancreatitis</td>
</tr>
<tr>
<td>Reinisch et al, 2010&lt;sup&gt;4&lt;/sup&gt;Austria, Czech Republic, Germany, Israel</td>
<td>Mesalazine</td>
<td>31</td>
<td>31 patients with Crohn’s disease (15 treated with mesalazine)</td>
<td>8 weeks treatment</td>
<td>0/15 (0%) had severe stenosis</td>
</tr>
<tr>
<td>Rasmussen et al, 1987&lt;sup&gt;5&lt;/sup&gt;</td>
<td>Pentasa (mesalazine)</td>
<td>67</td>
<td>67 CD patients (30 treated with Pentasa)</td>
<td>16 weeks treatment</td>
<td>No serious adverse events were reported</td>
</tr>
<tr>
<td>Martin et al, 1990&lt;sup&gt;6&lt;/sup&gt;</td>
<td>Salofalk (mesalazine)</td>
<td>50</td>
<td>50 CD patients (19 treated with 5-ASA)</td>
<td>12 weeks treatment</td>
<td>Of those treated with Salofalk 1/19 (5.3%) had viral hepatitis</td>
</tr>
<tr>
<td>Tremaine et al, 1994&lt;sup&gt;7&lt;/sup&gt;</td>
<td>Mesalazine</td>
<td>38</td>
<td>38 patients with Crohn’s disease (20 treated with mesalazine)</td>
<td>16 weeks</td>
<td>No serious adverse events were reported</td>
</tr>
<tr>
<td>Andus et al, 1995&lt;sup&gt;8&lt;/sup&gt;</td>
<td>Salofalk (mesalazine)</td>
<td>31</td>
<td>31 patients with Crohn’s disease (15 treated with 5ASA)</td>
<td>8 weeks treatment</td>
<td>Of those treated with Salofalk 1/15 (6.7%) had severe stenosis</td>
</tr>
<tr>
<td>Winship et al 1979&lt;sup&gt;9&lt;/sup&gt; USA RCT</td>
<td>Sulphasalazine</td>
<td>604</td>
<td>604 people with CD</td>
<td>4 years</td>
<td>0/132 (0%) withdrew due to pancreatitis</td>
</tr>
</tbody>
</table>
### Observational 5-ASA adverse event data

<table>
<thead>
<tr>
<th>Study type, reference, country</th>
<th>Drug</th>
<th>No with Crohn’s disease</th>
<th>Total number</th>
<th>Follow up</th>
<th>Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malchow et al, 1984&lt;sup&gt;10&lt;/sup&gt; Europe RCT</td>
<td>Sulfasalazine</td>
<td>452</td>
<td>452 CD patients (117 randomised to sulfasalazine)</td>
<td>6 weeks</td>
<td>Of those treated with sulfasalazine the incidence per 100 patient months was:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>treatment</td>
<td>2.46 for hypertension&lt;br&gt;0.006 for leukopaenia</td>
</tr>
<tr>
<td>De Jong et al, 2005&lt;sup&gt;11&lt;/sup&gt; The Netherlands Observational</td>
<td>Mesalazine/sulfasalazine</td>
<td>153</td>
<td>153 patients with CD (152 taking mesalazine, sulfasalazine or mixed 5-ASA)</td>
<td>Mean 8.6 years treatment</td>
<td>1/152 (0.66%) renal tuberculosis&lt;br&gt;1/152 (0.66%) pyelonephritis&lt;br&gt;2/152 (1.3%) obstructing urolithiasis</td>
</tr>
</tbody>
</table>
### 1.1.2 5-ASA safety data: serious adverse events in people with inflammatory bowel disease

<table>
<thead>
<tr>
<th>Study</th>
<th>Region</th>
<th>Study Design</th>
<th>Treatment</th>
<th>Duration</th>
<th>Outcomes</th>
</tr>
</thead>
</table>
| Jick et al, 1995¹²             | UK                    | Observational| Sulfasalazine/mesalamine | 14,376   | For the IBD population: No cases of blood disorders in those taking mesalamine  
For those taking sulfasalazine:  
0/6286 (0%) agranulocytosis  
2/6286 (0.03%) neutropenia  
0/6286 (0%) leukopenia  
1/6286 (0.02%) pancytopenia  
0/6286 (0%) thrombocytopenia  
1/6286 (0.02%) haemolytic anaemia |
| Hutfless et al, 2007¹³        | USA                   | Observational| Aminosalicylates   | 9032     | In those with CD being treated with aminosalicylates (n = 2566):  
175/2566 (6.8%) died (age- and sex-adjusted OR compared with those not taking 5-ASA = 0.9 (0.6 to 1.2)  
Of these deaths the causes of mortality were related to: digestive disease in 24 cases; infection in 21 cases; intestinal cancer in 9 cases; and lymphatic and haematopoietic cancers in 3 cases |
| Elseviers et al, 2004¹⁴       | Belgium, France, Italy, Macedonia, Yugoslavia | Observational| Sulfasalazine/5-ASA | 1529     | In those using 5-ASA:  
1/765 (0.13%) had end stage renal disease (focal glomerulosclerosis)  
7/765 (0.92%) had chronic renal failure  
12/765 (1.6%) had intermittent renal failure |
| Poulou et al, 2006¹⁵          | Greece                | Observational| 5-ASA              | 86       | No differences were found in levels of mALB and tubular microproteinuria between IBD patients who received or did not receive 5-ASA therapy.  
No differences were found between duration of |
Observational 5-ASA adverse event data

<table>
<thead>
<tr>
<th>Study</th>
<th>Drug</th>
<th>Treatment</th>
<th>Duration</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zelissen et al.1988</td>
<td>Salazosulfapyridine</td>
<td>11</td>
<td>4 months</td>
<td>8/11 (72.7%) oligospermia</td>
</tr>
</tbody>
</table>

5-ASA treatment and levels of mALB (for CD patients $p = 0.70$)

Treatment with 5-ASA was not correlated to the severity of microproteinuria or to the changes in creatinine clearance.
1.1.3 **Summary**

- Expected incidence of renal dysfunction (< 2%) appears to be overestimated in these large cohort studies of patients with Crohn’s disease.
- Serious pancreatitis occurred in approximately 1%.
- Cytopenias occurred in less than 0.05%.
- Oligospermia occurred at a rate of 73% (in a small study of sulfasalazine) indicating that it is the most important clinically significant adverse event associated with sulfasalazine.
1.1.4 Reference List


Observational 5-ASA adverse event data


