NCGC National Clinical Guideline Centre

Crohn's disease

Appendix L

Clinical Guideline <...>

5-ASA adverse-event data

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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

1.1.1 5-ASA safety data: serious adverse events in people with Crohn's disease

Study type, reference, country	Drug	No with Crohn's disease	Total number	Follow up	Events
Pure CD population					
Singleton et al, 1993[1] Multicentre RCT	Mesalazine	310	310 CD patients (230 treated with mesalazine)	16 weeks treatment	No serious adverse events were reported in either group, but note that only events occurring in > 1% of patients are recorded
Sutherland et al, 1997[2] Denmark Observational	Mesalazine	293	293 patients with Crohn's disease (CD; 141 taking mesalazine)	48 weeks treatment	1/141 (0.7%) with pancreatitis (that caused withdrawal)
McLeod et al, 1995[3] Canada and USA RCT	Mesalazine	163	163 CD patients (87 in treatment group)	72 months treatment	1/87 (1.1%) pancreatitis
Reinisch et al, 2010[4]Austria, Czech Republic, Germany, Israel RCT	Mesalazine	78	78 CD patients (37 treated with mesalazine)	12 months	0/37 (0%) pancreatitis 2/37 (5.4%) hypotension
Rasmussen et al, 1987[5] Denmark RCT	Pentasa (mesalazine)	67	67 CD patients (30 treated with Pentasa)	16 weeks treatment	No serious adverse events were reported
Martin et al, 1990[6] RCT	Salofalk (mesalazine)	50	50 CD patients (19 treated with 5-ASA)	12 weeks treatment	Of those treated with Salofalk 1/19 (5.3%) had viral hepatitis
Tremaine et al, 1994[7] RCT	Mesalazine	38	38 patients with Crohn's disease (20 treated with mesalazine)	16 weeks	No serious adverse events were reported
Andus et al, 1995[8] Multicentre RCT	Salofalk (mesalazine)	31	31 patients with Crohn's disease (15 treated with 5ASA)	8 weeks treatment	Of those treated with Salofalk 1/15 (6.7%) had severe stenosis
Winship et al 1979[9] USA RCT	Sulfasalazine	604	604 people with CD	4 years	0/132 (0%) withdrew due to pancreatitis

Study type, reference, country	Drug	No with Crohn's disease	Total number	Follow up	Events
Malchow et al, 1984[10] Europe RCT	Sulfasalazine	452	452 CD patients (117 randomised to sulfasalazine)	6 weeks treatment	Of those treated with sulfasalazine the incidence per 100 patient months was: 2.46 for hypertension 0.006 for leukopaenia
De Jong et al, 2005[11] The Netherlands Observational	Mesalazine/ sulfasalazine	153	153 patients with CD (152 taking mesalazine, sulfasalazine or mixed 5-ASA)	Mean 8.6 years treatment	1/152 (0.66%) renal tuberculosis 1/152 (0.66%) pyelonephritis 2/152 (1.3%) obstructing urolithiasis

1.1.2 5-ASA safety data: serious adverse events in people with inflammatory bowel disease

Mixed IBD population					
Jick et al, 1995[12] UK Observational	Sulfasalazine/mesalazine	14,376	10,330 patients with IBD; 6286 on sulfasalazine; 4044 on mesalazine	NA - retrospective	For the IBD population: No cases of blood disorders in those taking mesalazine 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, 2007[13] USA Observational	Aminosalicylates	9032	9032 patients with IBD (3241 with CD; 5238 with UC; 553 with both) vs health plan members without IBD 79% of those with CD took aminosalicylates	NA - retrospective	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, 2004[14] Belgium, France, Italy, Macedonia, Yugoslavia Observational	Sulfasalazine/5-ASA	1529	1529 IBD patients (56% had CD; during the study period 50% used 5-ASA and 9% used sulfasalazine)	1 year	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, 2006[15] Greece Observational	5-ASA	86	86 IBD patients (25 with CD; 46 received 5-ASA)	Mean 28.8 months	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

					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.
Zelissen et al,1988[16] The Netherlands Observational	Salazosulfapyridine	11	11 IBD patients (taking salazosulfapyridine as maintenance for a mean of 7.7 years)	4 months treatment	8/11 (72.7%) oligospermia

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

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