NCGC National Clinical Guideline Centre

Crohn's disease

Appendix M

Clinical Guideline <...>

Immunosuppressive safety data

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1 Observational data on adverse events associated with immunosuppressives

Risks of particular concern to the GDG were quantified by a review of observational studies as below:

General risks of immunosuppressives include:

- Lymphoproliferative disorders (risk between 2- and 5-fold normal risk)
- Cervical dysplasia (risk 1.7-fold normal). Crohn's disease does not preclude patients from receiving the HPV vaccine and patients should be encouraged to comply with the national vaccination programme.

1.1 Azathioprine and mercaptopurine

Common or serious risks of treatment with azathioprine and mercaptopurine include:

- Myelosuppression (1 – 4% in adults, rising to 7% in children)
- Acute pancreatitis (1%)
- Hepatitis (10%)
- Opportunistic Infections (3 – 6%).

1.2 Methotrexate

Common or serious risks of treatment with methotrexate include:

- Pneumonitis (2%)
- Hepatitis (20%)
- Opportunistic Infections (3 – 6%).

1.2.1 Immunosuppressive adverse-event data

Serious adverse events: immunosuppressives			
Study type, reference, country	Drug	Total N	Events
Armstrong et al, 2010 UK	AZA	15,471 people with inflammatory bowel disease	41 people with Crohn's disease who ever used AZA developed cancer/392 total number of people with inflammatory bowel disease who developed cancer Diagnosis of lymphoma was associated with ever use of AZA with OR (3.22 (95% CI 1.01-10.18)
Bastida et al, 2005 Spain	AZA/MP	161 people with inflammatory bowel disease	16/161 (9.9%) with hepatotoxicity
Beaugerie et al, 2009 France	Thiopurines	11,759 people with Crohn's disease (CD)	Lymphoproliferative disorders: Hazard ratio of LD 5.28 (2.01 to 13.9, p = 0.0007). Cases matched the pathological range of post-transplant disease
Bermejo et al, 2008 Spain	AZA/MP	5053 people with inflammatory bowel disease	Acute pancreatitis in 1.6% of patients with 63.4% attributed to AZA/MP (46 cases) CD vs UC for risk of AZA/MP induced AP OR 5.8 (1.6 to 20.6)
Bernstein et al, 1994 USA	MP	57 people with inflammatory bowel disease	16/27 (28%) mild leukopenia after 3 months No WBC < 2.8 x 103/mm3
deJong et al, 2004 Netherlands	AZA/MP	50 people with confirmed Crohn's disease	3/50 (6%) with infection 2 (4%) myelosuppression 1 pancreatitis and 1 elevated amylase (4%)
Domeneche et al, 2006	MTX	44 people with Crohn's disease	13/44 (29.5%) hepatotoxicity (elevated liver function tests)

Serious adverse events: immunosuppressives			
Spain			
Farrell et al, 2000 Republic of Ireland	AZA or MTX	782 people with inflammatory bowel disease; 238 received immunosuppressives	Non Hodgkin's lymphoma: 4 cases of NHL all of whom had received immunosuppressives Immunosuppressive group had 59 times higher risk of NHL than the general population.
Fuentes et al 2003 (Children with IBD) Italy	High-dose AZA	107 children with inflammatory bowel disease; 18 discontinued for clinical indications	8/107 children(7.5%) with bone marrow toxicity 3/18 (2.8%) with recurrent viral infection
Hutfless et al, 2007 USA	Immunosuppressives	3241 people with Crohn's disease	Mortality OR 1.3 (0.9 to 2.0)
Kandiel et al, 2005 USA	AZA/MP	1992 people with Crohn's disease	Lymphoma Pooled RR 4.18 (2.07 to 7.51) 11 observed cases; 2.63 expected cases
Lemann et al, 2000 France	Methotrexate	49 patients with Crohn's disease	10/49(20%) patients with liver abnormalities 1/49 (2%) with pneumonitis
Lewis et al, 2001 UK	AZA/MP	6605 people with Crohn's disease	Using GP data from 1988-1997, no (0) patients developed cancer/837 total people with Crohn's disease who ever used AZA Combining people with Crohn's disease and ulcerative colitis treated with AZA/MP the standardised incidence ratio for lymphoma was 1.57 (95% CI 0.04-8.75)
Marehbian et al, 2009 USA	Immunosuppressives	22,310 CD vs 111,550 general population	Solid tumours RR 1.68 (1.55 to 1.83) Cervical dysplasia RR 2.13 (1.86 to 2.44)

Serious adverse events: immunosuppressives			
			Lymphoma RR 1.66 (0.95 to 2.88) Opportunistic infection RR 3.63 (2.36 to 5.57) Sepsis RR 1.28 (1.16 to 1.40)
Masunaga et al, 2007 Japan	AZA/MP	1824 people with Crohn's disease with immunosuppressives vs. 11.428 without immunosuppressives	Malignancy RR -0.5 (1.2 to 0.3)
Setshedi et al, 2011	AZA/MP	123 people with IBD who received thiopurine therapy	Non-melanoma skin cancer was significantly associated with thiopurine exposure – OR5.0 (95% CI 1.1-22.8).
Prescrire International, 2011 France	AZA/MP	8676 people with inflammatory bowel disease exposed to AZA/MP; 10,810 people with inflammatory bowel disease never exposed	22 people developed non-Hodgkin's lymphoma and 1 person developed Hodgkin's disease. The risk of developing lymphoma was RR 3.75 (1.59-8.85) in people with Crohn's disease exposed to AZA/MP vs. those who had never taken either drug. After adjustment for age, sex, length of illness the risk increased to RR 5.26 (2.20-12.6).
Vos et al, 2011 Netherlands	AZA/MP	17,834 people with inflammatory bowel disease	44 lymphomas were observed, RR 1.27 (0.92-1.68) 19/44 people were exposed to AZA/MP. 92% of people (11/12) with EBV positive lymphoma used AZA/MP.