The long-term risk of continuous immunosuppression using thioguanides in inflammatory bowel disease

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Abstract: The efficacy of thiopurine treatment in the induction, and especially maintenance, of remission in inflammatory bowel disease is well proven; however, it is associated with side effects in both medium and long-term use. The potential harmful effects may be anticipated and minimised by due diligence prior to commencing these drugs followed by close monitoring of haematological and biochemical parameters once started. Careful clinical examination and history taking are also essential. Affected patients are expected to lead lives that include travel, employment and pregnancy – the implications of continued thiopurine therapy in such patients are discussed.

Keywords: azathioprine, mercaptopurine, immunomodulator, Crohn's disease, ulcerative colitis, inflammatory bowel disease, immunosuppression, lymphoma

Introduction

Thiopurines have been a mainstay in treating inflammatory bowel disease (IBD) for over a quarter of a century. The most commonly used agents in the management of IBD are azathioprine (AZA) and mercaptopurine (MP). AZA is a prodrug which undergoes metabolism to MP. The unique bioactivity of the thiopurines however gives them a specific therapeutic index that must be considered when they are used. The adverse event profile of these drugs is related to their active metabolites, most notably 6-thioguanine (6-TG) and 6-methylmercaptopurine (6-MMP). These reactions are catalysed by two enzymes, namely thiopurine methyltransferase (TPMT) and hypoxanthine phosphoribosyltransferase. Their use is limited by serious adverse events leading to discontinuation of the drug in 9 to 25% of patients [Gearry and Barclay 2005; Gearry *et al.* 2004].

Adverse events associated with AZA and MP include nausea, allergic reaction, flu-like illness, malaise, fevers, rash, abdominal pain, pancreatitis, hepatotoxicity and myelosuppression. An increased risk of lymphoma has also been described [Beaugerie *et al.* 2006; Kandiel *et al.* 2005; Dubinsky, 2004]. A double-blind study in 1980 first illustrated the utility of MP in the

management of Crohn's disease (CD) [Present *et al.* 1980]. AZA has been used for CD since the 1960s [Brooke *et al.* 1969] and its efficacy of AZA for the management of ulcerative colitis (UC) was established in a double-blind controlled trial in 1982 [Kirk and Lennard-Jones, 1982], which showed a reduction in activity index and dose of prednisolone required at 6 months. It has since gone on to be a valuable agent in the management of CD and a systematic review has confirmed the utility of both AZA and MP in inducing remission in this condition [Sandborn *et al.* 2000]. Another review reinforced the use of thiopurines as an option for maintaining remission with improved response seen at higher doses and a greater steroid-sparing effect [Pearson *et al.* 2000]. A systematic review of studies comparing AZA and MP showed both are effective for maintenance of remission in CD but that higher response rates were obtained with AZA than MP. In this study, patients who received AZA and MP were at greater risk of withdrawal from the study due to adverse events compared to those on placebo therapy. The number needed to harm (NNH) for AZA was 20. Withdrawals due to adverse effects were noted in 6% of patients receiving AZA therapy, 19% of patients receiving MP therapy and 3% of placebo patients [Prefontaine *et al.* 2009].

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Table 1. Adverse events with thiopurine therapy.

Infection	Viral: HSV varicella HPV varicella Tuberculosis PCP
Liver toxicity	Nodular regeneration Cholestasis Drug-induced hepatitis Viral hepatitis
Lymphoma	Non-Hodgkin's Usually EBV-related Background risk in IBD
Other malignancy	Cervical dyskaryosis Other malignancy uncommon
Bone marrow suppression	7% experience some; severe effect in 1.1%
Fertility and pregnancy	Consider risk vs benefit Safe for pregnant women Teratogenicity rare in males Breastfeeding probably safe No effect on fertility

EBV, Epstein-Barr virus; HPV, human papilloma virus; HSV, herpes simplex virus; IBD, inflammatory bowel disease; PCP, pneumocystis carinii pneumonia.

In this article, we aim to address the major classes of adverse event associated with long-term thiopurine therapy in patients with IBD (Table 1). This must be considered in the light of the relevant demographics of this group. For instance, the majority of patients are diagnosed between the ages of 20 and 40 and therefore may be exposed to the drugs for prolonged periods of time and in many cases coincides with the years of greatest reproductive potential. Many also are taking a combination of immunomodulators including thiopurines, steroids and anti-tumor necrosis factor (TNF)- α agents. Combination therapy has been proven to lead to an increase in the rates of complications particularly opportunistic infections [Toruner *et al.* 2008]. Understanding the negative implications of thiopurine therapy is essential for those undergoing long-term treatment of IBD and those providing it.

TPMT testing

TPMT catalyses the metabolism of the thiopurine drugs into their active components. TPMT enzyme activity is a major factor in determining AZA and MP metabolism, and therefore 6-TG and 6-MMP levels. Therefore, it is feasible that the therapeutic efficacy, bone marrow toxicity, and liver toxicity of these drugs may be predicted by testing levels of TPMT prior to the commencement of therapy. The TPMT genotype and phenotype (enzyme activity levels) both

have clinical relevance. Nine out of 10 people are homozygous for the gene that regulates TPMT and this is associated with good TPMT activity. The majority of the rest of the population are heterozygotes with intermediate TPMT activity [Lennard *et al.* 1993, 1989]. Such patients are less likely to benefit and more likely to accrue harm from thiopurine use. 1 in 300 of the population is homozygous for mutations of TPMT which is a more sinister phenomenon and these patients will have negligible TPMT activity, resulting in considerably higher levels of 6-TG and subsequently are at great risk of myelosuppression. Even within the 'normal' metabolizers there can be up to a three-fold difference in initial target doses of AZA and MP to achieve therapeutic 6-TG concentrations [Gardiner *et al.* 2008].

The main tools used to plan treatment are TPMT genotyping and phenotyping. Genotyping for TPMT genetic polymorphisms may be useful and has been shown to be cost effective in IBD patients, however it lacks consistency and may not identify many of the patients who go on to develop myelotoxicity. A paediatric study illustrated the benefit of identifying those likely to need high doses to induce remission by means of genotyping and phenotyping [Cuffari *et al.* 2004]. Another study looked at whether AZA dose selection based on pharmacogenetic testing of TPMT and metabolite monitoring offered a safety and

efficacy advantage over traditional dosing strategies. This was proven to be beneficial with TPMT being more beneficial for predicting the dose required for initial response to treatment and metabolite monitoring being more beneficial for predicting sustained response to treatment [Dubinksky *et al.* 2005]. The cost effectiveness of testing was shown in a further project in which pretreatment genotyping cost £347 (British Pounds sterling) per life-year saved for a 30-year old and £817 per life-year saved for a 60 year old [Winter *et al.* 2004]. However, studies have lacked consistency and may not predict a substantial number of those who will develop myelosuppression. One study of 41 patients who developed myelotoxicity after AZA use showed that only 27% had mutant alleles of the TPMT gene associated with enzyme deficiency which would have been detectable at genotyping [Colombel *et al.* 2000]. In terms of cost effectiveness, genotyping does not seem to predict those at risk of developing myelotoxicity after a prolonged period of use and studies have suggested that more prolonged periods of monitoring of haematological parameters are required than had hitherto been thought necessary [Qasim *et al.* 2003]. With regard to phenotyping, it has been proposed that a quantitative analysis of TPMT activity can guide doses with those with absent activity being precluded from receiving the drug and increasing doses given efficacious and safe with higher levels of TPMT activity [Cuffari *et al.* 2004].

Infection

Patients with IBD have many factors that may predispose them to opportunistic infections, such as the lack of an appropriate innate immune response to infectious agents (a response that may be inherent in the disease), malnutrition, surgery and immunosuppressive medication [Korzenik, 2007; O'Sullivan and O'Moráin, 2006]. The rate of opportunistic infection in patients with IBD has never been properly quantified but it is clear that increasing levels of immunosuppressive therapy increase the incidence of infection. Thiopurines, due to their effect on lymphocyte apoptosis may have a particular predilection for causing infection with viral pathogens such as cytomegalovirus (CMV), varicella zoster virus (VZV) or the Epstein–Barr virus (EBV).

40% of patients newly diagnosed with IBD will require immunomodulators at some point in their disease course with the vast bulk of these

being treated for at least some time with a thiopurine. In a cross-sectional cohort of 20,000 patients in France in 2004–2005, more than half of the patients with CD were ever treated with AZA while about one quarter of the patients with UC had received AZA at some juncture [Beaugerie *et al.* 2006]. One study of 169 patients with IBD on AZA and 61 controls not on an immunosuppressant examined the rates of respiratory, herpes simplex virus (HSV) and cutaneous human papilloma virus (HPV) (wart) infection. Rates of respiratory infection were equivalent across both groups, although the incidence of HSV flares and HPV warts was greater in the AZA group [Seksik *et al.* 2009]. Another study of patients on 6-MP which retrospectively examined 396 patients over a mean period of 5 years showed infectious complications occurring with a rate of 7.4% of which 1.8% were severe, including one instance of herpes zoster encephalitis. A similar study on 410 patients treated with MP revealed a 14% rate of infectious complications, including pneumonia in 3.9% and herpes zoster in 3%. A recent publication looking at over 22,000 patients with CD found a higher rate of infection with tuberculosis, herpes zoster, sepsis (as well as demyelination and cervical dysplasia) amongst patients on thiopurines, which is increased by combined regimens of immunomodulation with steroids and/or anti-TNF- α agents [Marehbian *et al.* 2009]. Hepatitis B infection is looked at in greater detail later in the article.

As there is a greater risk of vaccine-preventable illnesses in patients with IBD, the role of vaccination in the management of IBD patients must be developed. Recent guidelines from the European Crohn's and Colitis organisation (ECCO) have suggested a more aggressive programme of screening and vaccination at time of diagnosis for IBD patients including Varicella, pneumococcal, hepatitis B and HPV vaccines with both seasonal and pandemic influenza vaccines also recommended [Rahier *et al.* 2009]. Live vaccines, however such as yellow fever and poliomyelitis, should be avoided in IBD patients taking thiopurines [Advisory Committee on Immunization Practices, 1993]. This is an important consideration in the predominantly youthful and mobile IBD populations who are more likely to live in the western world and frequently present for travel vaccination. The same issues are prevalent however with other immunomodulators used in IBD also.

Liver toxicity

Hepatotoxicity has long been associated with thiopurine therapy. This tends to be a dose-related phenomenon as demonstrated by two trials which measured metabolite levels correlated to hepatotoxicity [Dubinsky *et al.* 2000; Cuffari *et al.* 1996]. The mechanisms of hepatic insult include a drug-induced hepatitis, cholestasis and nodular regenerative hyperplasia of the liver. A recent review found that the mean prevalence of AZA or 6-MP-induced liver injury in patients with IBD was approximately 3%, and mean annual drug-induced liver disorder rate was only 1.4% [Gisbert *et al.* 2007]. In a series of 396 IBD patients taking 6-MP, drug hepatitis was noted in 0.3%. Importantly, all of these events were reversible upon stopping the offending medication [Present *et al.* 1989]. Nodular regenerative hyperplasia (NRH) was first described among AZA users in a renal transplant cohort [Buffett *et al.* 1988]. Case reports have suggested that this can be associated with portal hypertension and even hepatocellular carcinoma in some IBD patients [Russmann *et al.* 2001; Arnott and Ghosh, 2000]. When a third pharmacologic agent, 6-TG (the actual active metabolite of the thiopurine family) was introduced it was thought that both efficacy and tolerability would be superior to the older agents, firstly due to its direct conversion to 6-thioguanine nucleotides (TGNs) and secondly its ability to produce high 6-TGN levels without producing high 6-MMP(R) levels. Nodular regenerative hyperplasia (NRH) though, was reported in very high levels in patients treated with this drug for IBD with one study reporting a 25% prevalence [Ferlitsch *et al.* 2007]. This was reproduced in another multicentre study [Seiderer *et al.* 2005] and a further study also concluded that the risk of NRH in patients taking 6-TG should preclude its use in patients with IBD [Dubinsky *et al.* 2003]. However, a more recent study of liver biopsies of thiopurine-naïve patients with IBD suggested a 6% prevalence of NRH even in this cohort and fibrosis and steatosis of varying degrees were detected in 31% and 36% of the liver biopsies respectively [de Boer *et al.* 2008a]. Another study suggested that using lower doses of 6-TG may maintain remission and carry a lower risk of NRH [de Boer *et al.* 2008b]. This may cause us to re-evaluate and weaken the association between NRH and these drugs in IBD patients.

Cholestasis can also occur and in contrast to the transaminitis induced by the drugs, this may not be reversible [Romagnuolo *et al.* 1998; Shorey *et al.* 1968]. Therefore, treatment should be

stopped in patients who develop severe hyperbilirubinaemia while on thiopurines. Concerns also arise about the role of thiopurines in managing patients infected with viral hepatitis. Currently, Hepatitis B virus (HBV) vaccination is recommended in all HBV-seronegative patients with IBD [Rahier *et al.* 2009]. There have not been any prospective studies on patients with IBD taking immunomodulators, but data derived from Hepatitis Bs antigen positive cancer patients shows that reactivation of HBV replication occurs in 20–50% of hepatitis B carriers undergoing immunosuppressive or cancer chemotherapy. Generally, these flares tend to be asymptomatic flares, but more complex cases including icteric flares, hepatic decompensation and death have been observed [Lok and McMahon, 2007]. Given the risks of hepatotoxicity inherent in using thiopurines for IBD the British Society of Gastroenterology recommends liver function testing weekly for 4 weeks when the drug is commenced or when the dose is increased. Once the dose, disease and blood monitoring is stable the frequency can be reduced to 3 monthly then yearly.

Lymphoma

Whether or not thiopurines increases the risk of neoplasia, remains controversial for the doses used to treat IBD although a significantly increased risk is reported in patients receiving high-dose AZA treatment following renal transplantation. The most common cancer reported in the literature in these patients is non-Hodgkin's lymphoma. Some of these have been reversible upon discontinuation of the drugs [Evans *et al.* 2008; Larvol *et al.* 1994]. A prospective cohort study of nearly 20,000 patients reported incidence rates of lymphoproliferative disorder of 0.90 per 1000 patient-years in those on thiopurines, 0.20/1000 patient-years in those who had discontinued thiopurine therapy, and 0.26/1000 patient-years in those who had never received thiopurines ($p = 0.0054$) [Beaugerie *et al.* 2006]. Many of the lymphomas reported in the literature have been associated with EBV and immunosuppression may well play a part in their pathogenesis. One study identified 18 cases of lymphoma in IBD patients over a prolonged period both before and after the widespread use of thiopurines to treat IBD. Six of the neoplasms occurred in patients treated with AZA or MP. Five of seven EBV-positive lymphomas occurred in patients treated with AZA or MP compared with one of 11 EBV-negative lymphomas [Dayharsh *et al.* 2002]. A number of studies have been done on

the risk of lymphoma but these have generally tended to be underpowered and conclusions have been conflicting. A meta-analysis was carried out on the relative risk of lymphoma among IBD patients treated with AZA or MP. This looked at six studies and found an approximate fourfold increased risk of lymphoma in IBD patients treated with AZA/MP. The authors postulated that this increased risk could be due to the medications, the severity of the underlying disease, or a combination of the two [Kandiel *et al.* 2005].

The underlying risk of lymphoma in patients with IBD has long been discussed. It has also been linked to IBD variants such as complicated anorectal disease and also is seen in colitis patients who develop colorectal cancer [Connell *et al.* 1994; Greenstein *et al.* 1992]. Naturally given the age profile of many IBD patients some concerns exist regarding long durations of therapy. A decision analysis using a Markov model was carried out and this showed that therapy with AZA to preserve remission in patients with CD results in overall increased quality-adjusted life expectancy. This increase was greatest in young patients who have the lowest baseline risk of non-Hodgkin's lymphoma and who have the greatest life expectancy in the absence of a CD-related death. However, in the modern era of anti-TNF- α combined immunomodulation this may need to be re-evaluated. Now that it has been shown that summative benefit may accrue from combinations of thiopurines and biologic agents [Sandborn, 2009], it is plausible that an increase in numbers of patients taking such regimens may lead to a rise in the number of lymphomas which may occur. A meta-analysis showed an incidence of lymphoma of 6.1 per 10,000 patient years in a cohort of patients who were treated with combination therapy of immunomodulator and anti-TNF- α compared to 4 per 10,000 years in those on immunomodulators alone and the expected rate of 1.9 per 10,000 patient years in the non-IBD population. The risk is statistically significant but low in absolute terms [Siegel *et al.* 2009]. Such a scenario emphasises the importance of multicentre and international collaborations in this field to better understand the risk of this rare but catastrophic side effect.

Other malignancies and cervical dyskaryosis

The risk of nonhaematogenous solid-organ malignancy in patients taking thioguanides for IBD does not appear to be significantly increased [Masunaga *et al.* 2007]. A nested case control

study of 15,471 patients did not reveal any increased risk of malignancy other than lymphoma [Armstrong *et al.* 2010]. However, in those on the medications following a renal transplant, there is a 50 to 100-fold increase in the relative risk of malignant disease [McKendry, 1991; Penn, 1990]. The most common tumours are squamous cell carcinomas of the skin, non-Hodgkin lymphoma, Kaposi's sarcoma, *in situ* carcinomas of the uterine cervix, and carcinomas of the vulva and perineum. Recently, it has been recommended that newly diagnosed females with IBD should receive HPV vaccination [Rahier *et al.* 2009]. It has been illustrated that female patients on all forms of immunomodulator therapy for IBD are significantly more likely to have abnormal cervical smears related to HPV infection [Kane *et al.* 2008]. The risk appears to increase with greater levels of immunosuppression with the risk of cervical abnormalities in women treated with thiopurines being increased by 30–40% among women who use these agents in addition to corticosteroids [Singh *et al.* 2009]. This is particularly concerning in the light of the knowledge that patients with IBD have markedly poor rates of attendance for cervical smears [Long *et al.* 2009]. This is possibly due to an overriding emphasis on the management of their symptomatic disease in their interactions with the health-care services, to the exclusion of other issues.

Bone marrow suppression

Thiopurines can cause myelosuppression in patients with low TPMT activity although it may also occur in the setting of normal TPMT activity. Up to a quarter of all patients taking thiopurines will experience some mild leucopenia, thrombocytopenia complicates 5% of cases. Dose-related marrow suppression results in leucopenia in up to 27% of patients and thrombocytopenia in up to 5% [Huskiison, 1984; Weinshilboum and Sladek, 1980]. When mild fluctuations in leucocyte levels occur, it is usually a reversible, dose-related phenomenon. Patients with low levels of TPMT activity are at greatest risk for myelosuppression. A meta-analysis on over 8000 patients showed the risk of outright myelosuppression to be a cumulative incidence of AZA/6-MP induced myelotoxicity to be 7% with an incidence rate (per patient and year of treatment) of 3% (95% confidence interval [CI] 3–4%). In this study, the risk was broadly the same with AZA as with MP (7% vs 9%). Of those who experienced myelotoxicity, the cumulative incidence of infection was 6.5%

Severe myelotoxicity was observed in 1.1%, with a 0.94% risk of death in all those who had myelotoxicity [Gisbert and Gomollón, 2008]. Interestingly, myelotoxicity occurred as soon as 12 days after treatment but up to 27 years. Another study looking at timing of myelotoxicity events in these patients though showed that the majority of events will still occur within the first 8 weeks of therapy. During this period the incidence of severe neutropenia and severe thrombocytopenia per 100 person-months was 0.51 and 0.08, respectively with a median duration from a normal white blood cell count to severe leukopenia or neutropenia of 13–14 days [Lewis *et al.* 2009]. The use of allopurinol for gout augments the risk of myelosuppression with numerous cases of profound pancytopenia reported [Kennedy *et al.* 1996; Venkat Raman *et al.* 1990].

An interesting aspect here is that in a selected cohort of patients with IBD who were taking AZA, the coprescription of allopurinol actually reduced the rate of hepatotoxicity. The lower rate of toxicity in patients on cotherapy might be attributable to the preferential shunting of AZA into the 6-TGN pathway when allopurinol is taken, as well as to the inhibition of reactive oxidative free radicals (ROS) that may cause tissue damage [Elion, 1989]. In practice, when thiopurines are commenced, low doses are usually used for the first week to test for drug hypersensitivity before increasing incrementally over a period of four to six weeks until the desired response is seen or a maximal total dose is reached, even though dose-independent mechanisms could be used. Weekly complete blood counts should be carried out during this time (including haemoglobin, mean cell volume, white blood cell count, and platelet count) and they should also be monitored every two weeks during dose escalation, and every four to six weeks after a stable dose is achieved for 3 months or more. Patients should also be advised to be vigilant for signs of infection and neutropenia and advised to seek medical assessment should such episodes occur [Furst and Clements, 1991].

Fertility and pregnancy

The United States Food and Drug Administration (FDA) has classified AZA as a Class D agent which means it is harmful to the foetus and should not be given during pregnancy without careful consideration of risk versus benefit. In practice, although MP and AZA cross the placenta and have been

found in cord blood, the human foetus is thought to be protected from the teratogenic effect of the thiopurines because the foetal liver lacks the enzyme inosinate phosphorylase which is necessary to convert AZA and MP to active metabolites [Habal and Ravindran, 2008]. Teratogenicity has been found in rodent models however, with skeletal and visceral abnormalities noted when doses equivalent to human ones are given [Burdett *et al.* 1988]. The evidence for teratogenicity of azathioprine when taken by the mother is limited to case reports [Williamson and Karp, 1981]. It has been illustrated by retrospective studies that these medications are safe in pregnant patients with IBD and if a patient is established on AZA or MP therapy and the drug is considered essential to maintain remission, the patient should continue treatment [Mahadevan and Kane, 2006; Francella *et al.* 2003; Alstead *et al.* 1990]. The effect of thiopurine use in the male parent on any potential teratogenicity is unclear [Tallent *et al.* 1970]. One, albeit small and unrandomised, study did suggest that the use of MP by the father in the three months prior to conception significantly increased the rate of pregnancy-related complications including spontaneous abortions and congenital abnormalities [Rajapakse *et al.* 2000]. Isolated reports have occurred of immunological and haematological complications in pregnancy including pancytopenia, lymphopenia, diminished immunoglobulin (Ig) G and IgM levels, cytomegalovirus infection, and a decreased thymic shadow in the children of mothers on concurrent AZA and high-dose corticosteroid therapy [DeWitte *et al.* 1984; Cote *et al.* 1974].

When the disease is inactive, fertility in the female patient does not appear to be compromised over and above those with IBD not on the medication [Mahadevan, 2006]. The major factor leading to decreased fertility in females has been undergoing surgery and this has been consistent across a number of studies. [Ording *et al.* 2002; Hudson *et al.* 1997]. Thiopurine use is not thought to modulate this risk in any way. Similarly, fertility in the male does not seem to be affected by these immunomodulators. One study of sperm density, motility and morphology in patients with IBD taking AZA without sulphasalazine showed no effect when compared to normal reference intervals [Dejaco *et al.* 2001]. As AZA and MP have been found in breast milk, breastfeeding is not recommended by the manufacturers of the agents. However, large scale clinical data is lacking. One small study of lactation in 8 women with IBD taking AZA showed that

the majority of the drug metabolite in breast milk is excreted within the first 4 h after drug intake. On the basis of maximum concentration measured, the infant ingests MP of <0.008 mg/kg bodyweight/24 h. The authors concluded that breastfeeding during treatment with AZA seemed safe and should be recommended, considering the extensive beneficial effects to mother and child [Christiansen *et al.* 2008]. A review of immunomodulators in pregnancy and breastfeeding came to the same conclusion [Gisbert, 2009]. More extensive studies are certainly warranted in this area.

Summary and recommendations

The potential benefits of thiopurine treatment in the induction, but primarily maintenance of remission in IBD are proven and trusted. However this comes with a certain price in terms of the side effects of medium and long term use. A strong therapeutic relationship and prompt access to medical opinion are essential for IBD patients taking these drugs. The potential harmful effects can be anticipated and minimised by due diligence prior to commencing the drug and close monitoring of haematological and biochemical parameters subsequent to commencement. Careful clinical examination and careful history taking also play a role here. Practitioners should remain cognisant of the life events that occur in these patients also with regard to travel, employment and pregnancy and anticipate the implications of this for the patients continued thiopurine therapy.

Conflict of interest statement

The authors declare they have no conflicts of interest.

References

- Advisory Committee on Immunization Practices (1993) Recommendations of the Advisory Committee on Immunization Practices (ACIP): use of vaccines and immune globulins in persons with altered immunocompetence. *MMWR Morb Mort Wkly Rep* 42(RR-4): 1–18.
- Alstead, E.M., Ritchie, J.K., Lennard-Jones, J.E., Farthing, M.J. and Clark, M.L. (1990) Safety of azathioprine in pregnancy in inflammatory bowel disease. *Gastroenterology* 99: 443–446.
- Armstrong, R.G., West, J. and Card, T.R. (2010) Risk of Cancer in Inflammatory Bowel Disease Treated With Azathioprine: A UK Population-Based Case-Control Study. *Am J Gastroenterol* Jan 26. [Epub ahead of print].
- Arnott, I.D. and Ghosh, S. (2000) Portal hypertension in the presence of minimal liver damage in Crohn's disease on long-term azathioprine: possible endothelial cell injury. *Eur J Gastroenterol Hepatol* 12(5): 569–573.
- Beaugerie, L., Carrat, F. and Bouvier, A.M. (2006) The use of immunomodulators and biologics in inflammatory bowel diseases (IBD): a cross-sectional French nationwide cohort 2004–2005. *Gastroenterology* 130(4 Suppl. 2): A2.
- Brooke, B.N., Hoffmann, D.C. and Swarbrick, E.T. (1969) Azathioprine for Crohn's disease. *Lancet* 20;2(7621): 612–614.
- Buffet, C., Cantarovitch, M., Pelletier, G., Fabre, M., Martin, E., Charpentier, B., Etienne, J.P. and Fries, D. (1988) Three cases of nodular regenerative hyperplasia of the liver following renal transplantation. *Nephrol Dial Transplant* 3(3): 327–330.
- Burdett, D.N., Waterfield, J.D. and Shah, R.M. (1988) Vertical development of the secondary palate in hamster embryos following exposure to 6-mercaptopurine. *Teratology* Jun;37(6): 591–597.
- Christensen, L.A., Dahlerup, J.F., Nielsen, M.J., Fallingborg, J.F. and Schmiegelow, K. (2008) Azathioprine treatment during lactation. *Aliment Pharmacol Ther* 15;28(10): 1209–1213.
- Colombel, J.F., Ferrari, N., Debuysere, H., Marteau, P., Gendre, J.P., Bonaz, B. *et al.* (2000) Genotypic analysis of thiopurine S-methyltransferase in patients with Crohn's disease and severe myelosuppression during azathioprine therapy. *Gastroenterology* 118(6): 1025–1030.
- Connell, W.R., Sheffield, J.P., Kamm, M.A., Ritchie, J.K., Hawley, P.R. and Lennard-Jones, J.E. (1994) Lower gastrointestinal malignancy in Crohn's disease. *Gut* 35(3): 347–352.
- Cote, C.J., Meuwissen, H.J. and Pickering, R.J. (1974) Effects on the neonate of prednisone and azathioprine administered to the mother during pregnancy. *J Pediatr* 85: 324–328.
- Cuffari, C., Theoret, Y., Latour, S. and Seidman, G. (1996) 6-Mercaptopurine metabolism in Crohn's disease: correlation with efficacy and toxicity. *Gut* 39: 401–406.
- Cuffari, C., Dassopoulos, T., Turnbough, L., Thompson, R.E. and Bayless, T.M. (2004) Thiopurine methyltransferase activity influences clinical response to azathioprine in inflammatory bowel disease. *Clin Gastroenterol Hepatol* 2(5): 410–417.
- Dayharsh, G.A., Loftus Jr, E.V., Sandborn, W.J., Tremaine, W.J., Zinsmeister, A.R., Witzig, T.E. *et al.* (2002) Epstein-Barr virus-positive lymphoma in patients with inflammatory bowel disease treated with azathioprine or 6-mercaptopurine. *Gastroenterology* 122(1): 72–77.
- de Boer, N.K., Tuynman, H., Bloemena, E., Westerga, J., Van Der Peet, D.L., Mulder, C.J. *et al.* (2008a)

- Histopathology of liver biopsies from a thiopurine-naïve inflammatory bowel disease cohort: prevalence of nodular regenerative hyperplasia. *Scand J Gastroenterol* 43(5): 604–608.
- de Boer, N.K., Zondervan, P.E., Gilissen, L.P., den Hartog, G., Westerveld, B.D., Derijks, L.J. *et al.* (2008b) Absence of nodular regenerative hyperplasia after low-dose 6-thioguanine maintenance therapy in inflammatory bowel disease patients. *Dig Liver Dis* 40(2): 108–113.
- Dejaco, C., Mittermaier, C., Reinisch, W., Gasche, C., Waldhoer, T., Strohm, H. *et al.* (2001) Azathioprine treatment and male fertility in inflammatory bowel disease. *Gastroenterology* 121(5): 1048–1053.
- DeWitte, D.B., Buick, M.K. and Cyran, S.E. (1984) Neonatal pancytopenia and severe combined immunodeficiency associated with antenatal administration of azathioprine and prednisone. *J Pediatr* 105: 625–628.
- Dubinsky, M.C., Lamothe, S., Yang, H.Y., Targan, S.R., Sinnett, D., Theoret, Y. *et al.* (2000) Pharmacogenomics and metabolite measurement for 6-mercaptopurine therapy in inflammatory bowel disease. *Gastroenterology* 118: 705–713.
- Dubinsky, M.C., Vasilias, E.A., Singh, H., Abreu, M.T., Papadakis, K.A. and Tran, T. (2003) 6-thioguanine can cause serious liver injury in inflammatory bowel disease patients. *Gastroenterology* 125: 298–303.
- Dubinsky, M.C. (2004) Azathioprine, 6-mercaptopurine in inflammatory bowel disease: pharmacology, efficacy, and safety. *Clin Gastroenterol Hepatol* 2(9): 731–743.
- Dubinsky, M.C., Reyes, E., Ofman, J., Chiou, C.F., Wade, S. and Sandborn, W.J. (2005) A cost-effectiveness analysis of alternative disease management strategies in patients with Crohn's disease treated with azathioprine or 6-mercaptopurine. *Am J Gastroenterol* 100(10): 2239–2247.
- Elion, G.B. (1989) The purine path to chemotherapy. *Science* 244: 41–47.
- Evans, S.J., Watson, D.K. and O'Sullivan, M. (2008) Reversible Hodgkin's lymphoma associated with Epstein-Barr virus occurring during azathioprine therapy for SLE. *Rheumatology* 47(7): 1103–1104.
- Ferlitsch, A., Teml, A., Reinisch, W., Ulbrich, G., Wrba, F., Homoncik, M. *et al.* (2007) 6-thioguanine associated nodular regenerative hyperplasia in patients with inflammatory bowel disease may induce portal hypertension. *Am J Gastroenterol* 102(11): 2495–2503.
- Francella, A., Dyan, A., Bodian, C., Rubin, P., Chapman, M. and Present, D.H. (2003) The safety of 6-mercaptopurine for childbearing patients with inflammatory bowel disease: a retrospective cohort study. *Gastroenterology* 124: 9–17.
- Furst, D.E. and Clements, P.J. (1991) Pharmacologic approaches. SAARDs-II, In: Klippel, J.H. and Dieppe, P.A. (eds). *Rheumatology*, St. Louis: Mosby, p. 18.
- Gardiner, S.J., Gearry, R.B., Begg, E.J., Zhang, M. and Barclay, M.L. (2008) Thiopurine dose in intermediate and normal metabolizers of thiopurine methyltransferase may differ three-fold. *Clin Gastroenterol Hepatol* 6(6): 654–660.
- Gearry, R.B., Barclay, M.L., Burt, M.J., Collett, J.A. and Chapman, B.A. (2004) Thiopurine drug adverse effects in a population of New Zealand patients with inflammatory bowel disease. *Pharmacoevidiol Drug Saf* 13(8): 563–567.
- Gearry, R.B. and Barclay, M.L. (2005) Azathioprine and 6-mercaptopurine pharmacogenetics and metabolite monitoring in inflammatory bowel disease. *J Gastroenterol Hepatol* 20(8): 1149–1157.
- Geller, S.A., Dubinsky, M.C., Poordad, F.F., Vasilias, E.A., Cohen, A.H. and Abreu, M.T. (2004) Early hepatic nodular hyperplasia and submicroscopic fibrosis associated with 6-thioguanine therapy in inflammatory bowel disease. *Am J Surg Pathol* 28: 1204–1211.
- Gisbert, J.P., González-Lama, Y. and Maté, J. (2007) Thiopurine-induced liver injury in patients with inflammatory bowel disease: a systematic review. *Am J Gastroenterol* 102(7): 1518–1527.
- Gisbert, J.P. and Gomollón, F. (2008) Thiopurine-induced myelotoxicity in patients with inflammatory bowel disease: a review. *Am J Gastroenterol* 103(7): 1783–1800.
- Gisbert, J.P. (2009) Safety of immunomodulators and biologics for the treatment of inflammatory bowel disease during pregnancy and breast-feeding. *Inflamm Bowel Dis* Nov 2. [Epub ahead of print].
- Greenstein, A.J., Mullin, G.E., Strauchen, J.A., Heimann, T., Janowitz, H.D., Aufses Jr, A.H. *et al.* (1992) Lymphoma in inflammatory bowel disease. *Cancer* 1;69(5): 1119–1123.
- Habal, F.M. and Ravindran, N.C. (2008) Management of inflammatory bowel disease in the pregnant patient. *World J Gastroenterol* 14(9): 1326–1332.
- Hudson, M., Flett, G., Sinclair, T.S., Brunt, P.W., Templeton, A. and Mowat, N.A. (1997) Fertility and pregnancy in inflammatory bowel disease. *Int J Gynaecol Obstet* 58(2): 229–237.
- Huskisson, E.C. (1984) Azathioprine. *Clin Rheum Dis* 10: 325.
- Kandiel, A., Fraser, A.G., Korelitz, B.I., Brensinger, C. and Lewis, J.D. (2005) Increased risk of lymphoma among inflammatory bowel disease patients treated with azathioprine and 6-mercaptopurine. *Gut* 54(8): 1121–1125.
- Kane, S., Khatibi, B. and Reddy, D. (2008) Higher incidence of abnormal Pap smears in women with inflammatory bowel disease. *Am J Gastroenterol* 103(3): 631–636.

- Kennedy, D.T., Hayney, M.S. and Lake, K.D. (1996) Azathioprine and allopurinol: the price of an avoidable drug interaction. *Ann Pharmacother* 30(9): 951–954.
- Kirk, A.P. and Lennard-Jones, J.E. (1982) Controlled trial of azathioprine in chronic ulcerative colitis. *Br Med J (Clin Res Ed)* 284(6325): 1291–1292.
- Korzenik, J.R. (2007) Is Crohn's disease due to defective immunity? *Gut* 56: 2–5.
- Larvol, L., Soule, J.C. and Le Tourneau, A. (1994) Reversible lymphoma in the setting of azathioprine therapy for Crohn's disease. *N Engl J Med* 331(13): 883–884.
- Lennard, L., Gibson, B.E., Nicole, T. and Lilleyman, J.S. (1993) Congenital thiopurine methyltransferase deficiency and 6-mercaptopurine toxicity during treatment for acute lymphoblastic leukaemia. *Arch Dis Child* 69(5): 577–579.
- Lennard, L., Van Loon, J.A. and Weinshilboum, R.M. (1989) Pharmacogenetics of acute azathioprine toxicity: relationship to thiopurine methyltransferase genetic polymorphism. *Clin Pharmacol Ther* 46(2): 149–154.
- Lewis, J.D., Abramson, O., Pascua, M., Liu, L., Asakura, L.M., Velayos, F.S. et al. (2009) Timing of myelosuppression during thiopurine therapy for inflammatory bowel disease: implications for monitoring recommendations. *Clin Gastroenterol Hepatol* 7(11): 1195–1201.
- Lok, A.S. and McMahon, B.J. (2007) Chronic hepatitis B. *Hepatology* 45: 507–539.
- Long, M.D., Porter, C.Q., Sandler, R.S. and Kappelman, M.D. (2009) Suboptimal rates of cervical testing among women with inflammatory bowel disease. *Clin Gastroenterol Hepatol* 7(5): 549–553.
- Mahadevan, U. (2006) Fertility and pregnancy in the patient with inflammatory bowel disease. *Gut* 55: 1198–1206.
- Mahadevan, U. and Kane, S. (2006) American gastroenterological association institute medical position statement on the use of gastrointestinal medications in pregnancy. *Gastroenterology* 131: 278–282.
- Marehbian, J., Arrighi, H.M., Hass, S., Tian, H. and Sandborn, W.J. (2009) Adverse events associated with common therapy regimens for moderate-to-severe Crohn's disease. *Am J Gastroenterol* 104(10): 2524–2533.
- Masunaga, Y., Ohno, K., Ogawa, R., Hashiguchi, M., Echizen, H. and Ogata, H. (2007) Meta-analysis of risk of malignancy with immunosuppressive drugs in inflammatory bowel disease. *Ann Pharmacother* 41(1): 21–28.
- McKendry, R.J.R. (1991) Purine analogues, In: Dixon, J. and Furst, B.E. (eds). *Second Line Agents in the Treatment of Rheumatic Diseases*, Marcel Dekker: New York.
- Ording, O.K., Juul, S., Berndtsson, I., Oresland, T. and Laurberg, S. (2002) Ulcerative colitis: female fecundity before diagnosis, during disease, and after surgery compared with a population sample. *Gastroenterology* 122(1): 15–19.
- O'Sullivan, M. and O'Moráin, C. (2006) Nutrition in inflammatory bowel disease. *Best Pract Res Clin Gastroenterol* 20: 561–573.
- Pearson, D.C., May, G.R., Fick, G. and Sutherland, L.R. (2000) Azathioprine for maintaining remission of Crohn's disease. *Cochrane Database Syst Rev* CD000067.
- Penn, I. (1990) Cancers complicating organ transplantation. *N Engl J Med* 323: 1767.
- Prefontaine, E., Sutherland, L.R., Macdonald, J.K. and Cepoiu, M. (2009) Azathioprine or 6-mercaptopurine for maintenance of remission in Crohn's disease. *Cochrane Database Syst Rev* CD000067.
- Present, D.H., Korelitz, B.I., Wisch, N., Glass, J.L., Sachar, D.B. and Pasternack, B.S. (1980) Treatment of Crohn's disease with 6-mercaptopurine. A long-term, randomized, double-blind study. *N Engl J Med* 302(18): 981–987.
- Present, D.H., Meltzer, S.J., Krumholz, M.P., Wolke, A. and Korelitz, B.I. (1989) 6-Mercaptopurine in the management of inflammatory bowel disease: short- and long-term toxicity. *Ann Intern Med* 111: 641–649.
- Qasim, A., Seery, J., Buckley, M. and O'Morain, C. (2003) TPMT in the treatment of inflammatory bowel disease with azathioprine. *Gut* 52(5): 767.
- Rahier, J.F., Ben-Horin, S., Chowers, Y., Conlon, C., De Munter, P. and D'Haens, G. (2009) European evidence-based Consensus on the prevention, diagnosis and management of opportunistic infections in inflammatory bowel disease. *Journal of Crohn's and Colitis* 3: 47–91.
- Rajapakse, R.O., Korelitz, B.I., Zlatanich, J., Baiocco, P.J. and Gleim, G.W. (2000) Outcome of pregnancies when fathers are treated with 6-mercaptopurine for inflammatory bowel disease. *Am J Gastroenterol* 95(3): 684–688.
- Romagnuolo, J., Sadowski, D.C., Lalor, E., Jewell, L. and Thomson, A.B. (1998) Cholestatic hepatocellular injury with azathioprine: a case report and review of the mechanisms of hepatotoxicity. *Can J Gastroenterol* 12(7): 479–483.
- Russmann, S., Zimmermann, A., Krähenbühl, S., Kern, B. and Reichen, J. (2001) Veno-occlusive disease, nodular regenerative hyperplasia and hepatocellular carcinoma after azathioprine treatment in a patient with ulcerative colitis. *Eur J Gastroenterol Hepatol* 13(3): 287–290.
- Sandborn, W., Sutherland, L., Pearson, D., May, G., Modigliani, R. and Prantera, C. (2000) Azathioprine or 6-mercaptopurine for inducing remission of Crohn's disease. *Cochrane Database Syst Rev* CD000545.

- Sandborn, W. (2009) One year data from the SONIC study: A randomized, double-blind trial comparing infliximab and infliximab plus azathioprine to azathioprine in patients with crohn's disease naive to immunomodulators and biologic therapy. *DDW*. Abstract 751f.
- Seiderer, J., Zech, C.J., Reinisch, W., Lukas, M., Diebold, J. and Wrba, F. (2005) A multicenter assessment of liver toxicity by MRI and biopsy in IBD patients on 6-thioguanine. *J Hepatol* 43(2): 303–309.
- Seksik, P., Cosnes, J., Sokol, H., Nion-Larmurier, I., Gendre, J.P. and Beaugerie, L. (2009) Incidence of benign upper respiratory tract infections, HSV and HPV cutaneous infections in inflammatory bowel disease patients treated with azathioprine. *Aliment Pharmacol Ther* 29(10): 1106–1113.
- Shorey, J., Schenker, S., Suki, W.N. and Combes, B. (1968) Hepatotoxicity of mercaptopurine. *Arch Intern Med* 122: 54.
- Siegel, C.A., Marden, S.M., Persing, S.M., Larson, R.J. and Sands, B.E. (2009) Risk of lymphoma associated with combination anti-tumor necrosis factor and immunomodulator therapy for the treatment of Crohn's disease: a meta-analysis. *Clin Gastroenterol Hepatol* 7(8): 874–881.
- Singh, H., Demers, A.A., Nugent, Z., Mahmud, S.M., Kliever, E.V. and Bernstein, C.N. (2009) Risk of cervical abnormalities in women with inflammatory bowel disease: a population-based nested case-control study. *Gastroenterology* 136(2): 451–458.
- Tallent, M.B., Simmons, R.L. and Najarian, J.S. (1970) Birth defects in child of male recipient of kidney transplant. *JAMA* 211: 1854–1855.
- Toruner, M., Loftus Jr, E.V., Harmsen, W.S., Zinsmeister, A.R., Orenstein, R., Sandborn, W.J. *et al.* (2008) Risk factors for opportunistic infections in patients with inflammatory bowel disease. *Gastroenterology* 134: 929–936.
- Venkat Raman, G., Sharman, V.L. and Lee, H.A. (1990) Azathioprine and allopurinol: a potentially dangerous combination. *J Intern Med* 228(1): 69–71.
- Weinshilboum, R.M. and Sladek, S.L. (1980) Mercaptopurine pharmacogenetics: monogenic inheritance of erythrocyte thiopurine methyltransferase activity. *Am J Hum Genet* 32: 651.
- Williamson, R.A. and Karp, L.E. (1981) Azathioprine teratogenicity: review of the literature and case report. *Obstet Gynecol* 58: 247–250.
- Winter, J., Walker, A., Shapiro, D., Gaffney, D., Spooner, R.J. and Mills, P.R. (2004) Cost-effectiveness of thiopurine methyltransferase genotype screening in patients about to commence azathioprine therapy for treatment of inflammatory bowel disease. *Aliment Pharmacol Ther* 20(6): 593–599.