J R Coll Physicians Edinb 2009; 39:100–6

CLINICAL

Azathioprine use in inflammatory bowel disease in South Durham – an insight into clinical practice

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ABSTRACT Azathioprine is the most common immunosuppressant used in the management of inflammatory bowel disease (IBD). Most of the available data on the effectiveness of this drug emerge from large university teaching hospitals, where there is a referral bias towards complex patients combined with a need for specialist expertise and early initiation of therapy. There are limited data on the use of azathioprine in district general hospitals in the UK, particularly related to efficacy and side effect profile, with concerns about its safety potentially contributing to a reluctance to commence treatment with the drug until late in the course of the disease. This audit was a retrospective case note review of patients attending gastroenterology clinics in South Durham over a decade (1997–2007). The population of the region is 250,000. The Rotherham IBD Database for County Durham was used to identify patients who had ever been exposed to azathioprine. Efficacy and side effect profile were determined. Remission was defined as being steroid-free at 12 months after starting azathioprine. Relapse was defined as active disease requiring steroids or surgical intervention after starting azathioprine. Of 400 patients with IBD, 58 were treated with azathioprine over the ten-year period (13.1%), 29/318 with ulcerative colitis (9.1%), and 29/82 with Crohn's disease (35.4%). Overall, 21/58 (36.2%) patients were found to be steroid-free within a mean period of five months' treatment. Among factors favouring response to treatment, a disease phenotype of Crohn's disease was the only significant one; age, sex, disease distribution and dose were not significant. 27.6% patients relapsed despite treatment, with the relapse rate being lower in ulcerative colitis. Although 47% patients reported some side effect, myelotoxicity was recorded in only 12%. This audit reflects the efficacy and safety of azathioprine when used in the district hospital setting, comparable to larger tertiary centres. Overall, the use is lower than at specialist centres, but this is likely to change with time.

KEYWORDS Azathioprine, inflammatory bowel disease

DECLARATION OF INTERESTS MJ McDonnell has no conflict of interest to declare. A Dhar has been a member of the BSG IBD Database group and has received unconditional financial support for attending meetings and for clinical research from a number of pharmaceutical companies, including honoraria for advisory work outside of NHS contractual time.

This work has been presented as a poster at the United European Gastroenterology Week meeting in Vienna, 2008.

Published online ***April 2009***

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INTRODUCTION

Azathioprine is widely used in the management of inflammatory bowel disease (IBD). The efficacy of azathioprine in inducing and maintaining remission in Crohn's disease (CD) has been confirmed in numerous clinical trials and meta-analyses; less data are available on its efficacy in ulcerative colitis (UC).[1–6] There are limited data on the comparison of remission and relapse rates in CD and UC and on the response related to the extent of disease. Fraser et al. demonstrated higher remission rates in UC than CD, with equal maintenance of remission in both groups.[1] However, other comparable studies in this area are currently lacking. In terms of disease distribution, some studies have demonstrated colonic distribution of CD to be significant in favouring remission with azathioprine, while others have not.[1,2,7–8]

In the UK, most IBD is managed in district general hospitals, with complex cases being referred to tertiary teaching hospitals. The use of immunosuppressants is greater at tertiary centres, in part due to lower thresholds for commencing therapy and more aggressive disease, which is refractory to steroid treatment, and because of specialist expertise. Concerns regarding adverse effects of the drug, particularly myelotoxicity, pancreatitis and hepatotoxicity, may influence the reluctance of physicians in district general hospitals to commence azathioprine earlier. There are very few reports of large-scale experience with azathioprine from

district general hospitals with a large number of patients over a long period of time. This audit aims to provide this data, using a comprehensive electronic IBD database in a well-defined cohort over a decade.

AIMS AND METHODS

The primary aim of this audit was to review the practice of using azathioprine in South Durham over a long period of time by various clinicians, both physicians and surgeons, who were looking after patients with IBD over the past ten years. We also aimed to compare our results with published reports from larger centres in the UK and worldwide, specifically looking at the comparative efficacy of azathioprine in the management of CD and UC. Our secondary aims were to look at the relationship between disease extent and response, predictors of induction and maintenance of remission, and the dose and optimum duration of treatment in relation to toxicity and relapse rates.

Patients

All patients with IBD who had received azathioprine in South Durham between 1997 and 2007 were identified from the Rotherham IBD database®. This Microsoft Access®-based electronic database holds the details of all patients with IBD in County Durham with a minimum dataset of 16 epidemiological and clinical parameters which were agreed to by the British Society of Gastroenterology IBD Database User Group. A complete case note review was then undertaken for patients who had received azathioprine, and data were recorded on a structured Microsoft Excel® proforma.

Data were analysed separately for the two disease subgroups of CD and UC. The extent of involvement of the disease was defined by a combination of colonoscopic, histological and/or radiological examination according to the Montreal classification, and the maximum extent of involvement recorded as the definitive extent of disease.[9] A clinic patient was defined by one attendance at the outpatient clinic over a 12-month period. The following groups of patients were excluded from analysis – patients lost to follow-up (defined as no clinic visit within the past two years) and patients with indeterminate colitis.

Indications for starting azathioprine, dosage and TPMT assay

The indications for starting treatment with azathioprine were divided into the following three groups: steroid-sparing effect, refractory disease and to maintain remission in frequent relapsers. The dose of azathioprine that was effective for a particular patient was defined as the dose in mg/kg/d which maintained remission for 12 months. An arbitrary division was made into two groups: ≤2 mg/kg/d and >2 mg/kg/d. The initial dose was also recorded to see if early onset side effects were dose-related. The number of patients who had a thiopurine methyltransferase (TPMT) enzyme assay carried out was also recorded, and results noted as normal, intermediate or low.

Efficacy of azathioprine

The clinical efficacy of azathioprine was recorded as either 'remission' or 'relapse'. Remission was defined in one of three ways: successful withdrawal from steroids within one year of commencing azathioprine, >50% reduction in the frequency of relapses over the first year of treatment in comparison with the year prior to starting treatment, and a reduction in mean C-reactive protein (CRP, mg/L) from baseline over the first year of treatment (as compared with mean baseline CRP over the year prior to treatment). Patients who remained on low-dose maintenance therapy with steroids were recorded as remission not achieved. The continued use of oral 5-aminosalicylic acid (5-ASA) compounds and Predfoam or 5-ASA enemas was allowed within the definition of remission. Relapse was defined as worsening of symptoms necessitating systemic steroid or surgical treatment.

Adverse events

The following adverse events were specifically recorded: gastrointestinal symptoms (abdominal pain, nausea, vomiting, diarrhoea), infections, myelotoxicity defined by leukopaenia (mean white cell count $<4.0 \times 10^9$ and/or a neutrophil count $<2.0 \times 10^9$ within the first three months of treatment), hepatotoxicity, pancreatitis, allergic reaction (fever with rash) and miscellaneous (any other symptoms not listed above). Furthermore, the number of patients in whom azathioprine needed to be discontinued owing to adverse events was recorded.

Statistics

Owing to the retrospective nature of the data, most of the results are mainly descriptive. A chi-squared test was used to analyse the effect of azathioprine on the reduction of steroid requirement in patients with IBD. Relationships of variables such as age, gender and disease types to response and relapse rates were analysed using chi-squared and logistic regression tests. Statistical analysis was performed using SSPS software on Microsoft Excel® and Prism®.

RESULTS

Patient demographics

The total number of patients attending the IBD clinic in South Durham over the past 10 years was obtained from the departmental database. Of the 400 patients with IBD in South Durham, there were 318 patients with UC (72.3%) and 82 with CD (18.4%). A total of 58 (13.2%) were treated with azathioprine: 29 with UC and 29 with CD. This equates to 9.1% of UC patients and 35.4% of CD patients treated. The mean age of patients treated with azathioprine was 39 years (range 11–70) with a male to female ratio of 2:3. The average duration of treatment was 22.4 months (range 8–57). Table 1 shows the distribution of azathioprine use according to the nature of the disease.

TABLE 1 Azathioprine use in relation to disease characteristics

Disease type	Disease distribution	Number (%)
Crohn's disease	Ileal disease (L1)	4 (11)
	Colonic disease (L2)	19 (66)
	Ileocolonic disease (L3)	6 (20)
Ulcerative colitis	Distal	7 (24)
	Left-sided/subtotal	10 (35)
	Pancolitis/total	12 (41)

TABLE 2 Indications for commencing azathioprine

Indication for treatment	Crohn's disease (n=29)	Ulcerative colitis (n=29)	Total (n=58)
Steroid-sparing	12 (41.4%)	9 (31.0%)	21 (36.2%)
Refractory disease	6 (20.7%)	5 (17.2%)	11 (19.0%)
Maintenance of remission in frequent relapsers	11 (37.9%)	15 (51.7%)	26 (44.8%)

Indications for commencing azathioprine

Most patients were started on azathioprine for the maintenance of remission of active disease prone to frequent relapses. Table 2 shows the distribution of the indications for commencing azathioprine.

TPMT activity and azathioprine dose

Thiopurine methyltransferase enzyme assay was carried out in 8/58 (13.8%) patients only. Of those recorded, all had normal TPMT activity. Five patients who had their TPMT activity measured experienced adverse effects. There was no discernible relationship between TPMT activity and adverse events. The paucity of TPMT assays reflects the introduction of this assay in the latter part of the study decade.

Interestingly, the median starting dose of azathioprine prescribed was only 1 mg/kg. The initiating dose varied from 0.5 mg/kg/d in some to 2.5 mg/kg/d in others. A wide variation in clinical practice was observed between clinicians, with a tendency to start with very low doses of 0.5–1.0 mg/kg/d in one hospital and a much higher starting dose of 2–2.5mg/kg/d in another hospital. Table 3 shows the distribution of azathioprine dosage across the two sites. The final maintenance dose of azathioprine was >2 mg/kg in 30 patients (15 with CD and 15 with UC) and <2 mg/kg in the remaining 25 patients (12 with CD and 13 with UC). The final dose was not available in three patients. No attempts were made to increase the dose to 3 mg/kg or more in any patient who had not responded. Adverse events were recorded in 17/30 (56.7%) patients taking high-dose azathioprine and 10/25 (40.0%) patients taking low-dose azathioprine. There was no statistically significant relationship between the dose of azathioprine and occurrence of adverse events.

TABLE 3 Starting dose of azathioprine

Starting dose of azathioprine (mg/kg)	Site A	Site B	Total
0.5	6 (20.1%)	1 (3.4%)	7 (12.1%)
1.0	16 (55.2%)	15 (51.7%)	31 (53.4%)
1.5	4 (13.8%)	3 (10.4%)	7 (12.1%)
2.0	0	8 (27.6%)	8 (13.8%)
2.5	0	3 (10.4%)	3 (5.2%)
Not documented	3 (10.4%)	0	3 (5.2%)

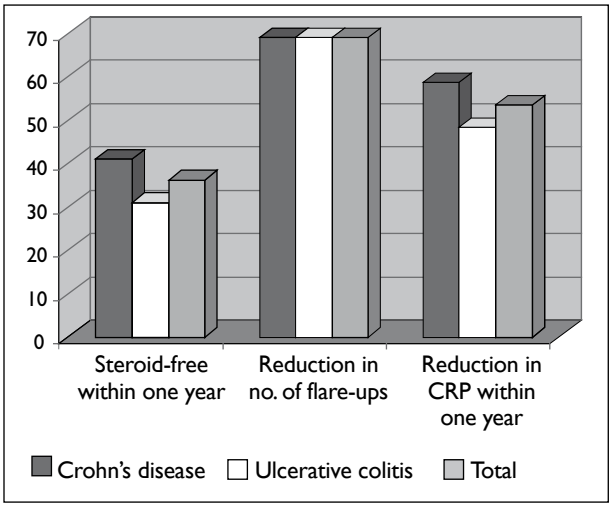

FIGURE 1 Remission rates with azathioprine.

Remission rates

Twenty-one out of 58 patients (36.2%) were found to be steroid-free within a mean time of five months; 41% of these patients had CD while 31% had UC. Forty out of 58 patients (69%) were noted to have a reduction in the number of flare-ups of their IBD within the first year of their treatment with azathioprine, with equal numbers of patients with CD and UC. There was no documentation with regard to the effects of flare-ups in 12/58 patients (20.7%), and six out of 58 patients (10.3%) showed no improvement with azathioprine.

Reduction from baseline CRP within the first year of treatment was achieved in 31/58 (53.4%) patients; 17/29 (58.6%) with CD and 14/29 (48.3%) with UC. The range of CRP before treatment was 3–299 mg/L and after treatment 3–76 mg/L. Eleven out of 58 patients (18.9%) did not show any improvement in baseline CRP and 16/58 (27.6%) did not have CRP results after their commencement of azathioprine. Figure 1 shows these results.

TABLE 4 Adverse events related to azathioprine

Major adverse events	Total number of patients	Number of patients in whom medication was discontinued
Hepatotoxicity	0	0
Pancreatitis	2	0
Myelotoxicity	7	1

Relapse rates

Fifteen out of 58 patients (25.6%) relapsed despite treatment with azathioprine in varying doses. Of those with CD, the relapse rate was 10/29 (34.2%); seven (24.1%) of these patients required surgical intervention and three (10.1%) required the reintroduction of systemic steroids. The relapse rate was considerably lower in patients with UC than CD.

Predictors of response

The nature of IBD seemed to have a trend towards predicting response to azathioprine, with CD patients showing a higher response than UC (41% vs 31%), but this did not reach statistical significance. Other factors that were not statistically significant for response to azathioprine were age, sex, disease distribution and dose. However, it must be noted that more patients with CD relapsed than with UC.

Adverse events

The overall adverse event rate was 27/58 (47%). Minor side effects were recorded in 13 patients (22.4%). Of these, eight had gastrointestinal side effects and five had miscellaneous symptoms (three with skin rash, one with hair loss and another with an abnormal shivering episode). All of these symptoms subsided within two weeks, and medication did not need to be discontinued (Table 4).

With regards to major adverse events, there was no incidence of clinical hepatotoxicity resulting in cessation of treatment in any patient in this cohort. Pancreatitis was reported in two patients, both of whom were noted to have a high level of alcohol intake, which is potentially another cause for pancreatitis, and so azathioprine was not discontinued. Myelotoxic effects were reported in 7/58 (12.1%) patients, with leukopaenia in four patients and neutropaenia requiring antibiotics in one patient. Azathioprine was only discontinued in the patient with neutropaenia and restarted at a later date. Time to onset of leukopaenia ranged between four and 14 weeks after initiation of treatment. The frequency of adverse events was similar in CD and UC.

Other indications for discontinuation of medication included non-response in 10 patients who subsequently underwent definitive surgery. One patient requested to stop the medication as they were feeling well and in remission. We did not find any patient who had developed haematological malignancies such as leukaemia or lymphoma in this audit. At the time of data collection, all 58 patients treated with azathioprine were alive and hence we do not attribute any excess mortality to the use of azathioprine over the period of observation.

DISCUSSION

This audit is a report of the clinical practice of azathioprine in the management of IBD in two district general hospitals in South Durham, northern England, over a ten-year period. It is a realistic report of the efficacy of the drug, its relative safety and the frequency of side effects, and relates to IBD practice outwith specialist centres. It eliminates bias related to consultant expertise, specialist training in IBD, physicians/gastroenterologists vs surgeons and referral. It is therefore a reflection of outcomes that can be expected by the average clinician encountering patients with IBD in district general hospitals in the UK.

The overall use of azathioprine in this cohort of 400 patients with IBD was 13.2%, which is slightly lower than the national figure of usage of 19% (personal communication from Dr Cathryn Edwards, Chair of the BSG IBD Database Committee) and the Oxford study, which reported 18.2% usage.[1] This is explained by various factors, including a much higher threshold to commence azathioprine in the earlier part of the decade as well as physician choice. Approximately three times as many patients with CD received azathioprine compared with UC patients in South Durham, and this compares well with other reports. However, many fewer patients with UC were treated with azathioprine compared with a tertiary centre such as Oxford (9% vs 26%), which is indicative of a preference for surgery in UC patients who did not respond to steroids in Durham.[1] Our response/remission rates compare favourably with published data on both CD and UC, with a total of 36.2% of patients being steroid-free within a year of treatment, 69.0% of patients experiencing a reduction in flare-ups over the first year of treatment and 53.4% achieving a reduction in baseline CRP over the first year of treatment.[1–11]

Our audit showed a steroid-free proportion of 36% and a reduction of flare-ups in 70% of patients, which is lower than reported figures in other studies. Ardizzone et al. reported that 70% of patients who had shown endoscopic and clinic remission in UC were able to stop steroids.[11] Pearson et al. demonstrated the same effect of azathioprine in CD, whereby 68% of patients who had shown improvement were no longer on steroids at the end of one year on azathioprine.[4] In a retrospective study by Khan et al. 68% of patients with IBD were steroid-free at one year.[2] Our result may in part be explained by the tendency to use smaller doses for induction and maintenance treatment in this cohort (mean dose of 1 mg/kg).

It is well known that the immunosuppressive effect of azathioprine is dose-dependent, with the usual dose of azathioprine being 2–2.5 mg/kg. In a large randomised trial, O'Donoghue et al. found a 2-mg/kg dose effective in maintaining remission.[5] In the meta-analysis of CD, Pearson et al. calculated an effective range of 2–3 mg/kg.[4] Yet some studies have shown a positive response to azathioprine at a lower mean maintenance dose of 1.5 mg/kg.[2] As another indicator of response to the drug, we compared the reduction in the number of flare-ups of IBD in the first year of treatment to the year prior to commencing azathioprine and found improvements in 69% of patients with equal incidence between CD and UC. This result is consistent with published data. Khan et al. demonstrated improvements in 74% of patients, and Hawthorne et al. showed similar results.[2,12] George et al. in a retrospective review using 6-mercaptopurine (6-MP) in 105 patients with UC demonstrated a remission rate of 65%, similar to our data.[12] Fraser et al. demonstrated remission rates of 64% and 87% in CD and UC respectively when looking at 414 patients treated with azathioprine over a six-month period in a large Oxford cohort of IBD.[1]

Reduction in CRP from baseline was also used as a marker of remission with improvement demonstrated in 53.4% patients. Although inflammatory markers are often used in clinical practice as laboratory markers to demonstrate improvement in disease activity, it must be noted that CRP may be influenced by other factors such as corticosteroid and antibiotic use and therefore its use as an independent marker of response to azathioprine may be limited.

In our audit, 25.6% patients relapsed despite treatment with azathioprine. Relapse was defined as worsening of symptoms necessitating additional systemic steroid therapy or surgery. The relapse rate was higher in CD than UC (34.2% vs 17.2%). This is similar to the relapse rate found in other studies.[1–3,11–12] Candy et al. randomised patients with CD to treatment with azathioprine plus prednisolone or prednisolone alone. The remission rates at 12 weeks were equal in both groups, but after 15 months 42% of patients receiving azathioprine achieved and maintained remission compared with 7% on placebo.[3] Hawthorne et al. studied 79 patients with UC who had been receiving azathioprine treatment for more than six months and were randomised to continuing treatment or withdrawal of treatment. The one-year relapse rate was 36% for patients who continued on azathioprine and 59% for patients who discontinued treatment.[12]

We also found that azathioprine was more likely to induce remission in CD than UC, but relapse rates were much lower in those with UC. This contrasts with the study by Fraser and colleagues, where remission rates were higher in UC but the maintenance of remission was equal in both groups.[1] In our study, there appears to be a trend suggesting better response rates with CD than UC (41% vs 31%), although this did not reach statistical significance. Age, sex, disease distribution and dose did not influence response to the drug. Other studies have shown male sex and older patients to be predictive factors for maintenance of remission.[1,5] A French study found no significant relationship between the site of disease involvement, but several other studies have demonstrated colonic distribution of CD to be significant in favouring remission with azathioprine.[1,7–8]

Uncertainties exist regarding factors predicting response to treatment with azathioprine. Neutrophil count has been identified in several studies over time as a predictor of the induction and maintenance of remission.[1,7,8,13] A recent case-control study in Canada identified male gender, initial presentation with severe disease, requirement of hospitalisation on diagnosis and the use of systemic steroids within six months of diagnosis to be predictive factors for azathioprine use in UC.[10] This contrasts with Fraser et al. who found gender to be significant in CD only and not UC.[1]

The mean duration of treatment with azathioprine in this audit was 22.4 months, with a range from eight to 57 months. The optimal duration of treatment with azathioprine in IBD remains controversial. Fraser et al. in a 30-year review concluded that longer treatment with azathioprine does not alter the risk of relapse after stopping treatment.[1] A previous retrospective study suggested that treatment for longer than three to four years was no better than withdrawal of azathioprine treatment.[7] However, a more recent European multicentre study demonstrated that a continuation of treatment beyond four years further improved clinical activity in CD and reduced steroid requirement in both diseases.[14] The main argument against longer treatment duration of azathioprine is a long-term increased risk of malignancy. Studies assessing the risk of malignancy in IBD have demonstrated conflicting results. Kandiel et al. in their meta-analysis described a four-fold increase in the risk of lymphoma in patients treated with azathioprine or 6-MP.[15] The recent CESAME study suggested a doubling in the risk of lymphoma in patients with IBD.[16] In contrast, several other studies, including a recent meta-analysis on the risk of malignancy with immunosuppressive drugs in IBD, have demonstrated no increased risk of malignancy following long-term treatment with azathioprine.[10,17,18]

Over the timescale of the study, there was no drug-related mortality. Adverse effects of azathioprine have been widely reported and have been the reason for physicians' concern. The overall adverse event rate in this audit was 27/58 (47%), perhaps reflecting the reality of practice outside the clinical trial setting. Nausea and vomiting did not appear to be dose-related and dose reduction did not make these adverse effects less

obvious. Minor side effects were reported in 22.4% of patients. Myelotoxicity occurred in 12.1% of patients in this audit. The incidence of leukopaenia was consistent with other studies (2–3.8%) as was the incidence of other side effects.[6,13] Pancreatitis seemed to occur less often than previously reported, although serum amylase was only obtained in patients complaining of epigastric pain. In the literature, pancreatitis has been reported in the order of 3–7% of cases.[19] Adverse events did not appear to be dose-related, and dose reduction did not make them less obvious. Although it has been reported that up to one third of patients may have to be withdrawn from treatment due to adverse effects, we had a much lower rate of withdrawal.[1,20,21]

Thiopurine-related adverse drug reactions are frequent, ranging from 5% up to 40% in both a dose-dependent and dose-independent manner.[22] Azathioprine and 6-mercaptopurine are both inactive pro-drugs that require intracellular activation into the active 6-thioguanine nucleotides (6-TGNs).[20,23,24] This metabolic process undergoes three different competitive pathways that are catalysed by three different enzymes: xanthine oxidase (XO), TPMT and inosine triphosphatase (ITPA), all of which exhibit genetic polymorphisms.[23] The relevant activities of these three enzymes determine the amount of active 6-TGN metabolites.

Thiopurine methyltransferase activity is genetically determined, varying in different ethnic populations and can be normal, intermediate or low.[20] Pharmacogenetic studies have found that adverse reactions such as neutropaenia occur more commonly in patients with low TPMT activity.[20,21,23,24] These patients can safely be treated with reduced doses of azathioprine, provided they are subject to close monitoring. Patients with intermediate TPMT activity are most likely to respond to azathioprine treatment, while those with very high TPMT activity may be resistant to standard doses of therapy.[20] Early adverse reactions such as nausea, vomiting, arthralgia and flu-like symptoms may be associated with polymorphisms in ITPA.[21] Pharmacogenetic polymorphisms in the 6-MP pathway may help to identify patients at risk of associated toxicities and serve as a guide for dose individualisation. Based on several cost–benefit analyses, an assessment of TPMT activity is recommended prior to initiating thiopurine therapy in patients with IBD.[22] The positive effects of azathioprine have to be balanced with its adverse effects. Some studies have defined factors such as TPMT co-administration of mesalazine and concomitant steroid use to predict susceptibility to adverse reactions to azathioprine.[23,25,26]

Azathioprine is an established medication for the treatment of IBD, but greater benefit may be obtained if prescribed at higher initial doses, thereby increasing the likelihood of inducing remission. Although this is a retrospective review and there are therefore some limitations to the study, long-term data are critical for clinical decision-making and are unlikely to be obtained from prospective data; further large-group population studies are needed to define this risk–benefit ratio.

The retrospective data in this audit also have some inherent limitations. Not all the necessary information could be obtained from patient case notes. The cohort is small in comparison to other similar studies and there is likely to be heterogeneity in prescribing between clinicians. The data presented reflect the clinical practice of these hospitals and extend over a long period, and we believe that this audit reflects the safety and efficacy of azathioprine in IBD in clinical practice outside of specialist centres in the UK and mirrors the experience of expert IBD clinicians in other parts of the world. This in itself is reassuring and should encourage more gastroenterologists to initiate treatment appropriately and in the correct dosage. A survey of British gastroenterologists in 1999 showed that there was marked variation in the duration of azathioprine use, with 46% of gastroenterologists using azathioprine for less than two years and only 17% continuing treatment for four years or longer.[27]

We conclude from our ten-year audit that azathioprine remains a safe and effective drug for the treatment of IBD. Although there are several recognised potential safety concerns regarding the use of azathioprine in IBD, this needs to be counterbalanced by objective decision-making, good risk–benefit counselling and a high clinical index of awareness of these potential problems. This audit should encourage confidence in gastroenterologists practising in district general hospitals to initiate early treatment using the recommended effective dosage to achieve high remission rates. Correlation to TPMT and other thiopurine metabolites could be structured in the future to allow clinicians to use azathioprine with greater confidence.

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