The efficacy of azathioprine for the treatment of inflammatory bowel disease: a 30 year review

A G Fraser, T R Orchard, D P Jewell

Background: There are limited data on factors predicting response to azathioprine and uncertainty regarding the optimal duration of treatment.

Patients and methods: The notes of patients attending the Oxford IBD clinic from 1968 to 1999 were reviewed. Remission was defined as no need for oral steroids for at least three months and relapse was defined as active disease requiring steroids.

Results: A total of 622 of 2205 patients were treated with azathioprine (272 Crohn’s disease, 346 ulcerative colitis, and four indeterminate colitis). Mean duration of the initial course of treatment was 634 days. The overall remission rates were 45% for Crohn’s disease and 58% for ulcerative colitis. For the 424 patients who received more than six months of treatment, remission rates were 64% and 87%, respectively. Factors favouring remission were ulcerative colitis (p=0.0001), lower white blood cell (WBC) or neutrophil count (p=0.0001), higher mean cell volume (p=0.0001), and older age (p=0.05). For Crohn’s disease, colonic disease favoured remission (p=0.03). Factors that were not significant were age, sex, lymphocyte count, and dose (mg/kg). The proportion of patients remaining in remission at one, three, and five years was 0.95, 0.69, and 0.55, respectively. The chance of remaining in remission was higher if WBC was less than 5 x 10^9 (p=0.03) and in male patients (p=0.01; Crohn’s disease only). There was no difference in relapse rates between Crohn’s disease and ulcerative colitis. After stopping azathioprine, the proportion of patients remaining in remission at one, three, and five years was 0.63, 0.44, and 0.35 (222 patients). Duration of azathioprine treatment did not affect the relapse rate after stopping treatment (p=0.68).

Conclusions: Azathioprine is effective treatment for ulcerative colitis and Crohn’s disease. The efficacy of azathioprine is reasonably well sustained over five years.

Azathioprine is widely used for the treatment of both Crohn’s disease and ulcerative colitis. Clinical trial data and a meta-analysis have confirmed the efficacy of azathioprine for Crohn’s disease. There are less efficacy data for ulcerative colitis and there are few data that have compared remission and relapse rates for ulcerative colitis and Crohn’s disease. There are some trial data that found that neutrophil count was a predictor of induction and maintenance of remission. This needs to be confirmed in a clinical audit as well as identifying other predictive factors for remission. It is unknown if longer duration of azathioprine treatment alters the risk of relapse after stopping treatment. A retrospective study suggested that treatment for longer than three to four years was no better than withdrawal of azathioprine treatment. There are no other comparable long term studies of the efficacy of azathioprine. These clinical questions cannot be answered easily by clinical trials but require audits of large clinic populations with careful and long term follow up.

Azathioprine is a purine analogue that competitively inhibits the biosynthesis of purine nucleotides. Its mode of action is not well understood. Once absorbed azathioprine is almost entirely metabolised to 6-mercaptopurine. There are two alternative pathways—one to 6-thiouric acid (mediated by xanthine oxidase) and the other to 6-methylmercaptopurine (mediated by thiopurinemethyltransferase). Low levels of thiopurinemethyltransferase lead to toxicity, particularly leucopenia. Uncertainty regarding the degree of risk from neutropenia deters some prescribers from using azathioprine at effective doses and for longer treatment durations. Side effects other than leucopenia also appear to limit the usefulness of this drug for a significant proportion of patients. Two types of side effects have been reported. Firstly, “allergic” non-dose related side effects which include pancreatitis, fever, rash, malaise, nausea, diarrhoea, and hepatitis. Secondly, there are “non-allergic” and presumably dose related side effects such as leucopenia and some forms of hepatitis. Although these side effects may be dose related, the genotype of the 6-thiopurinemethyltransferase enzyme is probably a more important determinant of developing leucopenia. Clinic data over a long term period of review gives a useful perspective of the clinical risk and toxicity of this drug.

METHODS
The notes of patients attending the Inflammatory Bowel Clinic at the John Radcliffe Hospital from 1968 to 1999 were reviewed. A clinic patient was defined by attendance at the outpatient clinic over a period of at least 12 months. Patients who had started azathioprine treatment at another hospital were excluded. Patients who received azathioprine primarily for other indications (renal transplant, rheumatoid arthritis, autoimmune liver disease) were excluded. Remission was defined as no need for oral steroids (either prednisolone or budesonide) for at least three months and a Harvey-Bradshaw score of 4 or less. Patients who were well on low doses of steroids were reported as “remission not achieved”. The continued use of oral 5-aminosalicylic acid compounds and steroid or 5-aminosalicylic acid enemas was allowed within the definition of remission. Relapse was defined as the need for reintroduction of steroids or the need for a surgical procedure. Relapse of short duration was defined as needing a course of steroids for less than three months while azathioprine was continued. The efficacy of azathioprine treatment was only assessed if treatment had been continued for six months or more. Patients were considered lost to follow up if there was no clinic visit within the last two years. Data were collected for...
azathioprine treatment only; 6-mercaptopurine was used sparingly in the Oxford Inflammatory Bowel Disease clinic. The extent of involvement of disease was defined by colonoscopic or radiological examination and not by histological evidence of inflammation. Diagnosis was based on data from the last clinical evaluation. Patients who continued to have a diagnosis of indeterminate colitis at the end of the follow-up period were combined with patients with Crohn’s disease.

The dose of azathioprine for the efficacy data (mg/kg) was defined as the maintenance dose that induced remission. The initial dose was also recorded to determine if “early onset” side effects were dose related. The definition of leucopenia was a white blood count <3×10⁹ and/or a neutrophil count of less than 2×10⁹. Neutropenia was considered to be due to chlorpromazine.

Statistical analysis was performed using SPSS version 9.0. The probabilities of relapse were calculated by life table analysis. The influence of concomitant variables on time to relapse was examined by the Cox proportional hazards model. Differences between means for continuous data were tested using analysis of variance.

**RESULTS**

The clinical notes of 2205 patients were reviewed; azathioprine treatment was given to 622 patients. There were 272 patients with Crohn’s disease, four with indeterminate colitis (combined with Crohn’s disease data in subsequent analysis), and 346 with ulcerative colitis. Mean duration of follow up from the start of azathioprine treatment was 2518 (1995) days (6.9 (5.5) years; mean (SD)). Mean follow up after diagnosis was 4943 (3395) days (13.5 (9.3) years; 8423 patient years of observation (four patients in each group). Two patients had significant pancytopenia. Mean duration of treatment before the onset of leucopenia was 421 days (range 47–1514). Five patients developed leucopenia in less than three months, seven patients in 3–6 months, three patients in 6–12 months, eight patients in 12–24 months, and five patients developed leucopenia after 24 months of treatment (the highest duration of treatment was 50 months). Nine patients had episodes of sepsis during azathioprine treatment that could be related to immunosuppression. Only four episodes of sepsis were related to neutropenia. Three patients required treatment with intravenous antibiotics and there was no mortality. Five patients had infective complications but did not have neutropenia. One patient presented with a sore throat and a large mouth ulcer with a nadir of neutrophils of only 2.3×10⁹. One patient had cytomegalovirus hepatitis, another had sacral herpes zoster infection, and two patients had generalised warts. Three patients (out of the 2205 patients with inflammatory bowel disease) had neutropenic sepsis related to other medications. Two patients had sulphasalazine induced pancytopenia (one patient had life threatening *Pseudomonas* septicaemia). Another patient died from neutropenic sepsis eight years after completing a four year course of azathioprine. Neutropenia was considered to be due to chlorpromazine.

Other reasons for discontinuation of medication were that the medication was considered to be ineffective (46), surgery become necessary (68), the patient was uneasy about the potential side effects and requested stopping the medication (41), or the patient conceived or wished to become pregnant while off the medication (seven).

**Induction of remission**

A total of 424 patients completed six months of azathioprine treatment. For these patients remission was achieved in 64% of patients with Crohn’s disease and 87% with ulcerative colitis (p=0.0001). Overall remission rates (including all patients treated with azathioprine) were 45% and 58% for Crohn’s disease and ulcerative colitis, respectively. Factors predictive of achieving remission are listed in table 1. Significant factors were a lower white blood count (p=0.0001), lower neutrophil count (p=0.0001), higher mean cell volume (p=0.0001), and an older age when treatment was given (p=0.05). Factors that were not significant were weight, dose of azathioprine (mg/kg), age at diagnosis, and lymphocyte count. For Crohn’s disease patients analysed separately, colonic disease was associated with a higher rate of remission (p=0.03). By multiple

| Table 1 Factors predicting remission on azathioprine treatment (mean and 95% confidence intervals) |
|--------------------------------------------------|-----------------|----------------|
| Remission achieved | Remission not achieved | p Value |
| Neutrophil count (<10⁹) | 3.83 (3.63,4.02) | 5.85 (5.28,6.42) | 0.0001 |
| WBC (<10⁹) | 5.86 (5.63,6.10) | 7.91 (7.32,8.51) | 0.0001 |
| MCV | 93.2 (92.1,94.2) | 88.8 (87.2,90.4) | 0.0001 |
| Age when Rx given | 38.0 (36.4,39.7) | 34.7 (32.0,37.5) | 0.05 |
| Weight (kg) | 69.8 (68.1,71.6) | 66.6 (63.6,69.7) | 0.07 |
| Age at diagnosis | 31.1 (29.6,32.7) | 28.7 (25.9,31.4) | 0.13 |
| Dose (mg/kg) | 1.65 (1.57,1.74) | 1.64 (1.59,1.68) | 0.74 |
| Lymphocyte count (<10⁹) | 1.33 (1.26,1.40) | 1.33 (1.15,1.50) | 0.96 |

WBC, white blood cell count; MCV, mean cell volume.

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remaining in remission during the treatment period (28 were for the 324 patients who achieved remission, 250 patients
(p=0.01) but were still independent factors in the model.

Table 2  Outcome while on azathioprine treatment for the 424 patients who were given treatment for more than six months

<table>
<thead>
<tr>
<th></th>
<th>Crohn’s disease</th>
<th>Ulcerative colitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>No relapse</td>
<td>91</td>
<td>159</td>
</tr>
<tr>
<td>Short relapse</td>
<td>16</td>
<td>26</td>
</tr>
<tr>
<td>Relapse</td>
<td>15</td>
<td>17</td>
</tr>
<tr>
<td>Remission not achieved</td>
<td>70</td>
<td>30</td>
</tr>
<tr>
<td>Total</td>
<td>192</td>
<td>232</td>
</tr>
</tbody>
</table>

logistic regression the independent factors in the model were
white blood count (or neutrophil count) (p=0.0001), diagnosis (Crohn’s disease or ulcerative colitis; p=0.001), and mean
cell volume (p=0.004). Mean cell volume and white blood
(count (or neutrophil count) were closely correlated (r=0.8,
p=0.01) but were still independent factors in the model.

Relapse
For the 324 patients who achieved remission, 250 patients
remained in remission during the treatment period (28 were
still continuing treatment at the time of follow up) (table 2).
Using a strict definition of relapse (including patients with a
short relapse), the proportion of patients still in remission at
12, 24, 36, 48, and 60 months was 0.95, 0.90, 0.69, 0.63, and
0.62, respectively (life table analysis; data for Crohn’s disease
and ulcerative colitis combined). If patients with “short
relapse” are included as “no relapse”, the proportion of patients
still in remission at 12, 24, 36, 48, and 60 months was 0.95, 0.90, 0.69, 0.63, and 0.62, respectively. Factors predictive
of remaining in remission (while still on treatment) were
determined by the Cox proportion hazards model. The relapse
rates were similar for ulcerative colitis and Crohn’s disease
(p=0.5) (fig 1). Patients with a minimum white blood count of

Figure 1  Cox regression analysis of the proportion of patients remaining in remission during azathioprine treatment related to
diagnosis of inflammatory bowel disease (324 patients). There was no difference in relapse rate between patients with ulcerative colitis and Crohn’s disease.

Figure 2  Cox regression analysis of the proportion of patients remaining in remission during azathioprine treatment related to
minimum observed white blood cell (WBC) count during treatment (324 patients). Patients with a WBC count of less than 5.0×10^9 were
more likely to remain in remission (p=0.03).

Table 3  Outcome after stopping azathioprine for 222 patients who were in remission at the time of stopping azathioprine

<table>
<thead>
<tr>
<th></th>
<th>Crohn’s disease</th>
<th>Ulcerative colitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>No relapse</td>
<td>16</td>
<td>36</td>
</tr>
<tr>
<td>Short relapse</td>
<td>14</td>
<td>28</td>
</tr>
<tr>
<td>Relapse</td>
<td>49</td>
<td>79</td>
</tr>
<tr>
<td>Total</td>
<td>79</td>
<td>143</td>
</tr>
</tbody>
</table>

Figure 3  Cox regression analysis of the proportion of patients remaining in remission after stopping azathioprine treatment related to diagnosis of inflammatory bowel disease (222 patients). There was no difference in relapse rate between Crohn’s disease and ulcerative colitis.

Figure 4  Cox regression analysis of the proportion of patients remaining in remission after stopping azathioprine related to
duration of azathioprine treatment (222 patients). There was no difference in relapse rate according to duration of treatment before stopping azathioprine.
receiving azathioprine achieved and maintained remission for patients with Crohn's disease to treatment with azathioprine only for a minority of patients. Appear to be dose related and dose reduction was successful at a lower dose was successful. Nausea and vomiting did not more common. Occasionally, retreatment at a later time and/or but without evidence of pancreatitis (normal amylase) was consistent with clinical trial data. Ongoing treatment make azathioprine a very valuable part of Crohn's disease and ulcerative colitis. The remission rates in patients with ulcerative colitis who had been receiving treatment for more than six months and were randomised to continuing treatment or withdrawal of treatment (67 patients were off steroids completely). The one year relapse rate was 36% (12/33) for patients continued on azathioprine and 59% (20/34) for patients who discontinued treatment. For patients in remission for more than six months the relapse rate on treatment was 31% (8/26) compared with 61% (17/28) for patients discontinuing treatment. In a similar retrospective review using 6-mercaptopurine in 105 patients with ulcerative colitis the remission rate was 65% (similar to this study). Life table analysis shows that maintenance azathioprine treatment is effective for up to five years of treatment. There is a gradual but acceptable increase in the proportion of patients who have relapsed over time. There is no suggestion that the effectiveness of treatment ‘wears out’ after a specific duration. There is no support for the concept that treatment should be stopped after 3–4 years (because it is no better than placebo). A French study of 157 patients with Crohn's disease in remission for at least six months compared the relapse rate of 115 patients who continued treatment with 42 patients who stopped treatment. The proportion remaining in remission at 12, 36, and 60 months was 0.89, 0.78, and 0.68, respectively. For the 42 patients who stopped treatment the proportion of patients still in remission at 12, 36, and 60 months was 0.62, 0.39, and 0.25, respectively. These data are remarkably similar to our data. The authors concluded that azathioprine was effective for at least four years but observed that the two year relapse rate after four years of treatment appeared to be similar whether treatment was continued or stopped. However, this observation was based on small numbers (only nine patients). O'Donoghue et al also reported a similar relapse rate of 41% one year after stopping treatment (proportion in remission 0.61). Data from our study using Cox proportional hazards modelling showed that there was no difference in relapse rates for patients treated for < 2 years, 2–4 years, or > 4 years duration.

Azathioprine is an established medication for the treatment of inflammatory bowel disease but there are many ways in which greater benefit can be obtained. Prescribing by a strict mg/kg schedule (at least 2 mg/kg) may increase the likelihood of giving a dose that will induce remission. The lack of dose-response seen in this study may be because treatment was given over a relatively narrow dose range and few patients were treated with recommended doses—up to 2.5 mg/kg.
Patients with Crohn’s disease frequently required surgery before completing a six month course of treatment. Many patients were operated on for obstructive symptoms that are less likely to respond to medical treatment. This is a justification for starting treatment early before irreversible fibrosis necessitates an operation for obstruction.

Increasing the duration of treatment will keep patients in remission for longer. A survey of British gastroenterologists showed that there was a marked variation in duration of use of azathioprine. Forty six per cent of gastroenterologists were using azathioprine for less than two years and only 17% were continuing treatment for four years or longer. Consultants with more experience of azathioprine in ulcerative colitis used azathioprine at higher maintenance doses for longer periods, and in patients with less extensive disease. The main argument against longer durations of treatment is the long term risk of malignancy. Connell et al observed no increased risk of malignancy in 755 patients with inflammatory bowel disease followed for a median of nine years from the start of azathioprine treatment. These are reassuring data but further studies from similar large clinic populations are required.

In summary, this study has shown good efficacy for azathioprine treatment sustained over at least five years with minimal toxicity and no mortality from neutropenic related sepsis over a 30 year review period.

References


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