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Long-term Efficacy and Safety of Azathioprine in Ulcerative Colitis

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Abstract

Background and aims: Azathioprine (AZA) is an established treatment for ulcerative colitis (UC). However, controversy exists regarding its efficacy in inducing and maintaining clinical remission, and long-term data are lacking. We studied the effectiveness of AZA in a large cohort of UC patients treated in a single center.

Methods: All UC patients treated with AZA were identified from a prospective electronic database. We assessed response to therapy at 4 months and sustained clinical benefit at the last point of follow-up. We also examined predictors of response and sustained clinical benefit, as well as outcomes in those treated with AZA for >5 years.

Results: The study included 255 patients. At 4 months, 207 (81.2%) of 255 patients were still on AZA and 163 (63.9%) had responded to therapy. At the last point of follow-up 164 (64.3%) patients were still receiving AZA, of whom 154 (60.4%) achieved sustained clinical benefit. This effect was durable among 71 patients who received AZA for >5 years, with 61 (85.9%) considered to have achieved sustained clinical benefit. Twenty-six patients required admission to hospital for an exacerbation during AZA treatment, 20 patients ultimately required biologic therapy, and 21 underwent colectomy. Only two (2.8%) of 71 patients receiving AZA for >5 years needed to escalate to a biologic therapy, and only one (1.4%) required a colectomy.

Conclusions: AZA is a safe and effective therapy in UC patients who fail 5-aminosalisylates in both the short and long term. Escalation to a biologic therapy or colectomy was unlikely among patients who were able to continue AZA therapy beyond 5 years.

Keywords: Azathioprine; thiopurine; immunomodulator; ulcerative colitis; efficacy; colectomy

1. Introduction

Ulcerative colitis (UC) is a chronic relapsing and remitting life-long condition, characterized by inflammation of the colonic mucosa. Its exact etiology remains obscure, but it is thought to arise from a combination of immune-mediated processes and environmental factors.[1] The disease is characterized by flares of disease activity, with periods of quiescence between these episodes. 5-Aminosalicylates (5-ASAs) are the mainstay of treatment for patients with mild to moderate flares,[2] as well as to maintain remission in patients with quiescent disease, with oral or intravenous glucocorticosteroids reserved for patients having more severe flares of disease activity.[3]

In those patients who become either dependent on or resistant to glucocorticosteroids, the next appropriate step may be immunomodulator therapies, such as azathioprine (AZA), a thiopurine analog.[4] However, although AZA is a well-established therapy in the treatment algorithm of Crohn's disease (CD) and has been shown to

be effective in the induction of and maintenance of remission of CD in several prospective, randomized controlled trials (RCTs),[5,6] the evidence base for its use in UC is not strong. Despite this, it is often used in clinical practice for the treatment of glucocorticosteroid-dependent or refractory UC, and this approach is recommended by international clinical guidelines.[4,7,8] A systematic review and meta-analysis of parallel-group RCTs showed no significant effect of AZA in inducing remission in active UC, although there was a statistically significant benefit of AZA in the prevention of relapse in quiescent UC.[9] However, the number of included studies was small and there was significant heterogeneity between them, highlighting the uncertainty in the available data.[10–12]

Partly due to this lack of evidence, some experts advocate that in those UC patients in whom clinical remission is not maintained with 5-ASAs, immediate escalation to a biologic is the next most appropriate management step.[13] However, some RCTs have reported only modest efficacy of biologics in UC, even during long-term therapy,[14,15] and these drugs are costly, whereas AZA is relatively inexpensive. Furthermore, biologics are only recommended in the UK by the National Institute for Health and Care Excellence (NICE) for inducing remission of an acute severe flare of UC not responding to glucocorticosteroids, and not for the long-term maintenance of remission, other than in exceptional circumstances. Azathioprine therefore continues to be the next-line treatment modality in the maintenance of remission in UC patients in the UK, where 5-ASAs are deemed to be ineffective. We have therefore examined the efficacy of AZA in UC, as well as outcomes in those who received the drug for 5 years or more, as data on the long-term efficacy of AZA in UC are sparse.

2. Methods

2.1. Data collection

The study was conducted at Leeds Teaching Hospitals NHS Trust (Leeds, UK), a large teaching hospital serving approximately 800 000 people in the north of England, which also receives tertiary referrals from other centers. All patients with UC who had been prescribed AZA at any point for the management of their UC were identified via a prospective electronic database maintained by our IBD nurse specialists. Those with an acute severe episode of UC activity who had received biologic therapies as a bridge to AZA therapy were excluded, as this may have altered the natural history of the disease, rather than AZA itself. The use of biologic therapies for chronic relapsing and remitting disease is not allowed routinely in our center, in line with NICE guidance. However, we are permitted to apply on an individual patient basis for the use of these drugs in this situation for compassionate reasons, if all other medical therapies have failed and the patient is faced with colectomy as the only remaining management option.

The following variables were recorded: age at diagnosis (in years), age at commencement of AZA (in years), gender, weight, thiopurine S-methyltransferase (TPMT) levels, duration of disease prior to commencing AZA (in months), concomitant oral or topical 5-ASA or glucocorticosteroid use at commencement of AZA, smoking status at diagnosis, presence of extra-intestinal manifestations, disease extent at diagnosis according to the Montreal classification,[16] and whether the patient's index presentation was with an acute severe episode of UC, as defined by symptoms necessitating hospital admission and treatment with intravenous glucocorticosteroids. All patients in our center with normal TPMT levels are commenced on AZA at a dose of 2.0–2.5 mg/kg/day. As we did not have access to thiopurine metabolite testing at the time of this study we did not adjust the dose routinely, unless there were adverse events or neutropenia occurred.

We also collected data on AZA dose, total treatment duration, whether the patient had shown a clinical response 4 months after commencing AZA, whether the patient remained on AZA at the last point of follow-up, and whether the patient achieved sustained clinical benefit at the last point of follow-up. The total number of flares of disease activity requiring oral glucocorticosteroid therapy, the number of UC-related hospital admissions, the need for escalation to biologic therapy, and the need for colectomy during follow-up were also recorded. Data regarding adverse events, reasons for discontinuation of AZA, and all new diagnoses of cancer were obtained. We also examined these endpoints in those who had received AZA for >5 years.

2.2. Outcomes

Our primary aims were to determine the short- and long-term efficacies of AZA therapy in UC by means of assessment of clinical response at 4 months following commencement of AZA and sustained clinical benefit at the patient's last point of follow-up. We used an assessment time point of 4 months for response to therapy, as this is in line with the RCT literature on the efficacy of immunosuppressants for induction of remission in UC.[11,17] As this was a retrospective study, it was not possible to determine response or remission by clinical indices, such as the Mayo scoring system for the assessment of ulcerative colitis activity.[18] Patients were therefore considered to have demonstrated a response if they were judged to be improving according to an evaluation of symptoms and hematologic, biochemical, and inflammatory parameters, as well as being able to taper oral glucocorticosteroids, and to have achieved sustained clinical benefit if they were well according to a physician's global assessment, which included an evaluation of symptoms and hematologic, biochemical, and inflammatory parameters, as well as complete withdrawal of oral glucocorticosteroids. Secondary aims of the study included assessing whether institution of AZA therapy led to a reduction in the frequency of harder endpoints, such as the need for UC-related hospitalization, escalation of therapy to a biologic, or the need for colectomy at any point after commencement of AZA therapy. We also examined the tolerability and safety of AZA by assessing the rates of adverse events that led to the cessation of AZA therapy, as well as serious adverse events, including infections and cancers. We examined all these endpoints only in patients who received AZA for >5 years.

2.3. Statistical analysis

Continuous variables were expressed as medians with the interquartile range and proportions were expressed as percentages. The statistical difference in the median age between responders and nonresponders was analyzed using the Mann–Whitney *U* test. Categorical variables were compared between responders and nonresponders using the χ^2 test. Predictors of response to AZA at 4 months and sustained clinical benefit at the last point of follow-up were explored using univariate and multivariate analysis, with results expressed as odds ratios (ORs) with 99% confidence intervals (CIs). Due to multiple analyses, a p value of <0.01 was considered statistically significant. All statistical analyses were performed using SPSS for Windows version 21.0 (SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Baseline patient characteristics

There were 255 patients (141 [55.3%] male, median age at diagnosis of UC 35 years [IQR 24–44 years]) with a diagnosis of UC who were prescribed AZA at any point through November 2012 and who were included in the study. Patient demographic and clinical

characteristics are shown in Table 1.There were 57 patients (22.4%) whose index presentation was with an acute, severe episode of UC, defined as symptoms necessitating hospital admission and needing intravenous glucocorticosteroids. Thirty-one (12.2%) patients had disease limited to the rectum (E1), 113 (44.3%) had disease distal to the splenic flexure (E2), and 111 (43.5%) had disease extending proximal to the splenic flexure (E3). Azathioprine was commenced at a median age of 42 years (IQR 29–53 years) within a median time of 24 months (IQR 8–84 months) following a diagnosis of UC. Concomitant medications are detailed in Table 1. The mean AZA dose at commencement was 1.7 mg/kg/day. The median duration of AZA treatment in all patients was 30 months (IQR 7–64.8 months), with a mean AZA dose at the last point of follow-up of 1.85 mg/kg/day. TPMT levels were checked in 232 (91.0%) patients. Eighteen (7.1%) patients had heterozygous TPMT deficiency.

3.2. Response to therapy at 4 months

Two hundred seven (81.2%) of 255 patients remained on AZA treatment at 4 months (Figure 1). Of these, 71 (34.3%) went on to receive the drug for >5 years, and 136 (65.7%) for ≤5 years. Of these 207 patients, 163 (63.9%) were considered to have achieved a clinical response. Only two of the 48 patients who had discontinued AZA at 4 months were considered to be nonresponders. Forty-six (18.0%) patients experienced adverse effects that resulted in AZA cessation (Table 2).

The median age at diagnosis in responders was 35 years (IQR 24–46 years) compared with 28.5 years (IQR 20–41 years) in nonresponders (p = 0.03). Nonresponders were more likely to be male (72.7% versus 52.1%, p = 0.02) and to have disease extending proximal to the splenic flexure (56.8% versus 39.9%, p = 0.04). Following univariate analysis, there were trends toward female gender (OR 0.41 for males versus females; 99% CI 0.16–1.07), higher age at diagnosis (OR 1.03 per year; 99% CI 1.00–1.06), lower weight (OR 0.98 per kg; 99% CI 0.96–1.01), and treatment with topical 5-ASAs (OR 3.17 for users versus nonusers; 99% CI 0.76–13.3) predicting the likelihood of response at 4 months (Table 3). However, following multivariate analysis, only the trend for weight remained (OR 0.97; 99% CI 0.94–1.01).

Table 1. Demographics of 255 patients with UC prescribed AZA.

Characteristic	All patients (n = 255)
Male, n (%)	141 (55.3)
Age at diagnosis, median (IQR), years	35.0 (24–44)
Smoker at diagnosis, n (%)	26 (10.2)
Index presentation with an acute, severe episode of UC n (%)	57 (22.4)
Disease extent, Montreal classification, n (%)	
Proctitis (E1)	31 (12.2)
Left-sided (E2)	113 (44.3)
Extensive (E3)	111 (43.5)
Extra-intestinal manifestations, n (%)	23 (9.0)
Age at AZA commencement, median (IQR), years	42.0 (29–53)
Duration of disease prior to AZA commencement, median (IQR), months	24 (8–84)
Concomitant treatments at commencement of AZA	
Oral glucocorticosteroids, n (%)	196 (76.9)
Oral 5-ASA, n (%)	222 (87.1)
Topical 5-ASA, n (%)	56 (22.0)
Duration of AZA treatment, median, (IQR), months	30 (7–64.8)
Heterozygous TPMT deficiency	18 (7.1)

3.3. Sustained clinical benefit at last point of follow-up

There were 164 (64.3%) of 255 patients who were still receiving AZA at the last point of follow-up, of whom 154 (60.4%) were considered to have achieved sustained clinical benefit (Figure 2). Among the 44 patients who had not responded to AZA at 4 months but who continued the drug, 28 (63.6%) went on to achieve sustained clinical benefit. The median age at diagnosis of patients who achieved sustained clinical benefit was 35 years (IQR 25–46 years), compared with 21.5 years (IQR 16–33 years) in those who did not (p = 0.007). Those not achieving sustained clinical benefit were more likely to have disease that extended proximal to the splenic flexure, although this was not statistically significant (60.0% versus 47.6%, p = 0.25). Higher age at diagnosis was the only predictor of sustained clinical benefit following univariate analysis (OR 1.03 per year; 99% CI 1.00–1.07) (Table 4). There were no statistically significant predictors following multivariate analysis. Of the 71 patients who had received the drug for >5 years, 61 (85.9%) were considered to have obtained sustained clinical benefit. A Kaplan–Meier analysis of the proportion of individuals with sustained clinical benefit up to 120 months is provided in Figure 3.

3.4. Need for escalation of therapy

Fifty (19.6%) of the 255 patients required one course of oral glucocorticosteroids during AZA therapy, 27 (10.6%) required two courses, and 26 (10.2%) required three or more courses. Twenty-six (10.2%) patients were admitted to hospital for a flare of UC requiring intravenous glucocorticosteroids, 20 (7.8%) required escalation to a biologic therapy, and 21 (8.2%) underwent colectomy during follow-up. In total, 50 (19.6%) patients experienced one or more of these three endpoints. Of the 71 who had received the drug for >5 years, 11 (15.5%) were admitted to hospital at any time during follow-up with a flare of UC requiring intravenous glucocorticosteroids, but only two (2.8%) needed to escalate to a biologic therapy and only one (1.4%) required a colectomy. Twelve (16.9%) patients experienced one or more of these three endpoints.

3.5. Outcomes following voluntary cessation of AZA

Seven patients discontinued AZA voluntarily as they felt clinically well. Six of these patients remained well, and were considered to have remained in clinical remission at the last point of follow-up. The mean duration of AZA treatment prior to cessation was 57.6 months (range 10–108 months). One patient relapsed following AZA cessation after 40 months of treatment and subsequently restarted AZA.

3.6. Adverse outcomes

A total of 74 (29.0%) patients experienced adverse events that resulted in AZA cessation. In 46 (18.0%) patients these occurred within 4 months of commencing AZA (Table 2). The most commonly occurring adverse events were myelotoxicity (7.1%), with one case resulting in sepsis and hospital admission within 1 month of commencing AZA, hepatotoxicity (5.5%), flu-like illness (5.1%), and gastrointestinal disturbances, predominantly nausea or vomiting (4.7%). There were three cases of nonmelanoma skin cancer (1.2%). Two of these patients continued AZA therapy following surgical

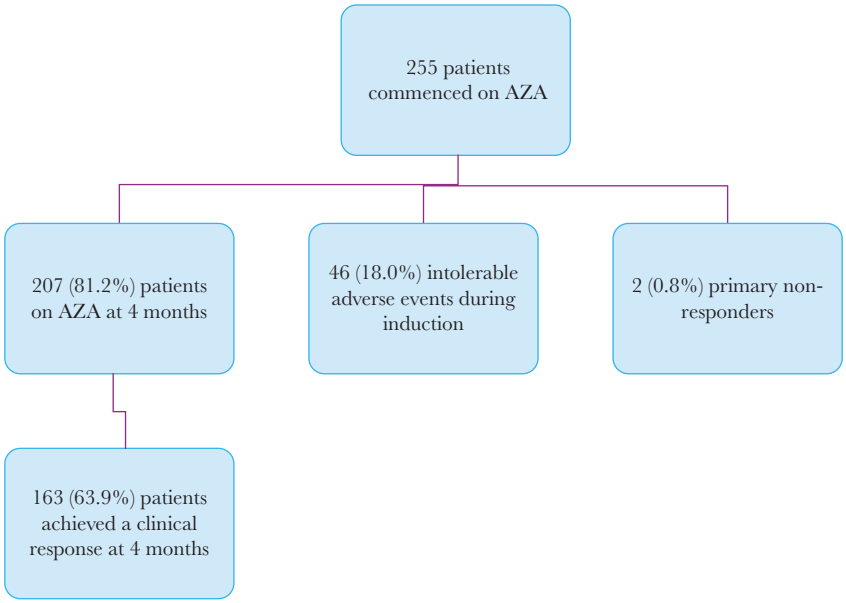

Figure 1. Clinical response to azathioprine at 4 months.

Table 2. Adverse events resulting in AZA cessation among 255 patients with UC during follow-up.

Adverse event	At 4 months (n = 255)	At last point of follow-up (n = 255)	Total (n = 255)
Myelotoxicity (%)	7 (2.7)	11 (4.3)	18 (7.1)
Hepatotoxicity (%)	9 (3.5)	5 (2.0)	14 (5.5)
Flu-like illness (%)	9 (3.5)	4 (1.6)	13 (5.1)
Gastrointestinal disturbance (%)	10 (3.9)	2 (0.8)	12 (4.7)
Acute pancreatitis (%)	5 (2.0)	1 (0.4)	6 (2.4)
Arthralgia/myalgia (%)	3 (1.2)	2 (0.8)	5 (2.0)
Dermatitis (%)	1 (0.4)	1 (0.4)	2 (0.8)
Nonmelanoma skin cancer (%)	0 (0)	1 (0.4)	1 (0.4)
Other nonspecific adverse events (%)	2 (0.8)	1 (0.4)	3 (1.2)
Total (%)	46 (18.0)	28 (11.0)	74 (29.0)

excision of the cancer. The mean duration of AZA treatment in the nonmelanoma skin cancer cases was 83 months. There was one case each of breast cancer, cerebral tumor, and colorectal cancer.

Among the 28 patients experiencing adverse outcomes resulting in AZA cessation 4 months after commencement, three occurred in patients receiving AZA for >5 years (one case each of hepatotoxicity, neutropenia, and nonmelanoma skin cancer). The remaining 25 cases occurred in patients receiving AZA for ≤5 years.

4. Discussion

This study has reported the short- and long-term efficacies as well as the safety of AZA, and assessed predictors of response and sustained clinical benefit in a cohort of 255 patients with UC treated at a large teaching hospital in the UK. We also assessed these endpoints in those who received the drug for >5 years. Almost two-thirds of patients who remained on AZA at 4 months achieved a clinical response, and at the last point of follow-up 60% were considered to have achieved sustained clinical benefit. We were unable to identify any predictors of response or sustained clinical benefit with AZA, other than a trend for lower weight. Azathioprine also remained effective in the long term, with no significant difference in sustained clinical benefit between those receiving AZA for >5 years and those receiving AZA for ≤5 years. Around 30% of patients stopped the drug due to intolerable adverse events. Almost 20% of patients experienced one or more of the three more rigorous endpoints of UC-related hospital admission, the need for escalation to biologic therapy, or the need for colectomy.

Strengths of this study include the number of patients treated, making this one of the largest single-center studies to assess the efficacy and safety of AZA in UC. Furthermore, this is one of the few studies to assess the effect of AZA treatment beyond 5 years on the natural history of the disease. Limitations of the study include the retrospective nature of data collection, in that it used the physician's global assessment to judge the clinical response at 4 months and sustained clinical benefit at the last point of follow-up rather than a more precise assessment tool, such as the Mayo scoring system for assessment of ulcerative colitis activity. However, our study also examined a number of harder endpoints, including the effect of AZA on the need for UC-related hospitalization, escalation to biologic therapy, and the need for colectomy.

The rate of sustained clinical benefit we observed is in keeping with another retrospective study of 346 UC patients treated with AZA conducted in the UK, which reported a remission rate of 58%.[19] However, considerable differences in efficacy have been reported in other studies, varying from approximately 40% to 95%.

Table 3. Predictors of response at 4 months following univariate and multivariate analysis in 255 patients with UC.

Variable	Unadjusted OR for response	99% CI	*p* value	Adjusted OR for response	99% CI	*p* value
Age at diagnosis (per year)	1.03	1.00–1.06	0.03	1.03	0.99–1.07	0.06
Duration of disease prior to AZA (per year)	1.00	0.995–1.00	0.64	1.00	0.99–1.00	0.68
Weight (per kg)	0.98	0.96–1.01	0.04	0.97	0.94–1.01	0.03
Gender						
Female	1.00			1.00		
Male	0.41	0.16–1.07	0.02	0.62	0.19–1.99	0.29
Smoker						
No	1.00			1.00		
Yes	2.36	0.32–17.2	0.27	1.25	0.15–10.7	0.79
Extra-intestinal manifestations						
No	1.00			1.00		
Yes	2.13	0.29–15.6	0.33	2.08	0.24–18.2	0.38
Oral 5-ASA						
No	1.00			1.00		
Yes	1.27	0.35–4.68	0.63	0.98	0.19–5.15	0.97
Topical 5-ASA						
No	1.00			1.00		
Yes	3.17	0.76–13.3	0.04	2.03	0.43–9.58	0.24
Oral prednisolone						
No	1.00			1.00		
Yes	0.51	0.16–1.61	0.13	0.50	0.13–1.90	0.18
Montreal classification						
E1	1.00		0.14	1.00		0.32
E2	0.98	0.20–4.76	0.97	0.64	0.94–4.34	0.55
E3	0.50	0.11–2.29	0.24	0.39	0.06–2.56	0.20
Acute severe presentation at diagnosis						
No	1.00			1.00		
Yes	1.38	0.45–4.22	0.46	1.49	0.40–5.57	0.43

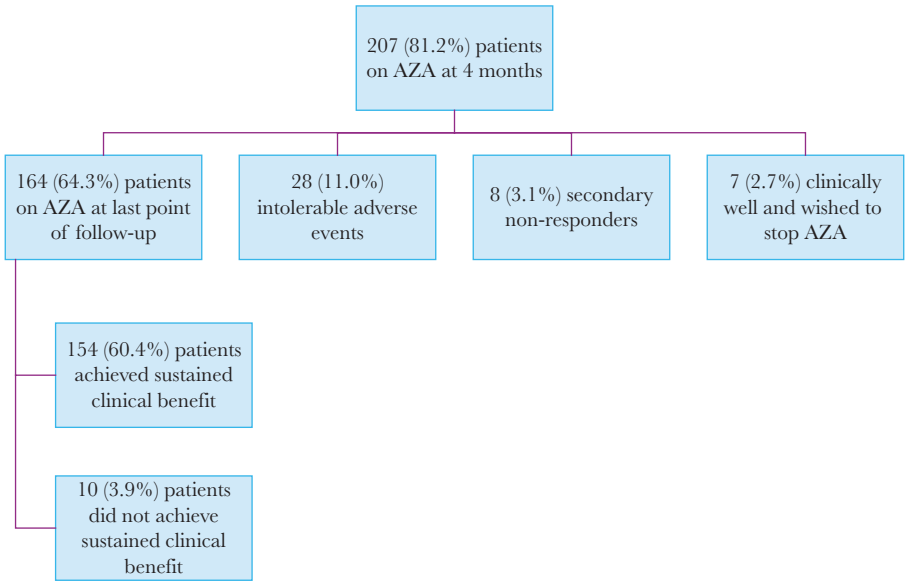

Figure 2. Sustained clinical benefit with azathioprine.

This disparity could partly be explained by the comparatively small number of participants in the majority of studies, as well as inconsistencies in the criteria used to define clinical response or remission.[20–23] A meta-analysis of 30 noncontrolled studies (n = 1632) and seven controlled studies (n = 213) evaluated the efficacy of thiopurine use in UC.[24] Pooled induction and maintenance of remission rates were 65% and 76% respectively for the noncontrolled studies and 73% and 60% respectively for the controlled studies. This is broadly in keeping with the results of our own study. However, as the authors of this meta-analysis acknowledged, there was significant heterogeneity between the studies, with limitations that included the small number of participants and relatively short duration of individual studies, highlighting the uncertainty in the available data.

Sixty-four patients received AZA for >5 years, making this one of the largest cohorts in which long-term outcomes of UC patients on AZA therapy have been examined. Our study shows a sustained clinical benefit of >85% in those patients still receiving AZA beyond 5 years, with only two of these patients needing to escalate

Table 4. Predictors of sustained clinical benefit at last point of follow-up following univariate and multivariate analysis in 255 patients with UC.

Variable	Unadjusted OR for sustained clinical benefit	99% CI	*p* value	Adjusted OR for sustained clinical benefit	99% CI	*p* value
Age at diagnosis (per year)	1.03	1.00–1.07	0.009	1.03	0.99–1.06	0.06
Duration of disease prior to AZA (per year)	1.00	0.996–1.004	0.99	1.00	0.99–1.00	0.38
Weight (per kg)	1.02	0.99–1.04	0.13	1.01	0.98–1.04	0.40
Gender						
Female	1.0			1.0		
Male	1.50	0.66–3.42	0.21	1.60	0.57–4.54	0.24
Smoker						
No	1.00			1.00		
Yes	1.31	0.29–6.00	0.65	1.09	0.20–6.04	0.90
Extra-intestinal manifestations						
No	1.00			1.00		
Yes	2.75	0.38–20.0	0.19	2.02	0.24–16.7	0.39
Oral 5-ASA						
No	1.00			1.00		
Yes	1.53	0.46–5.09	0.36	1.30	0.29–5.74	0.65
Topical 5-ASA						
No	1.00			1.00		
Yes	2.02	0.64–6.42	0.12	1.32	0.37–4.72	0.58
Oral prednisolone						
No	1.00			1.00		
Yes	0.64	0.23–1.76	0.25	0.67	0.21–2.17	0.38
Montreal classification						
E1	1.00		0.59	1.00		0.53
E2	0.80	0.19–3.34	0.68	0.78	0.14–4.21	0.70
E3	0.62	0.15–2.55	0.38	0.54	0.10–2.94	0.35
Acute severe presentation at diagnosis						
No	1.00			1.00		
Yes	0.57	0.22–1.45	0.12	0.44	0.15–1.35	0.06

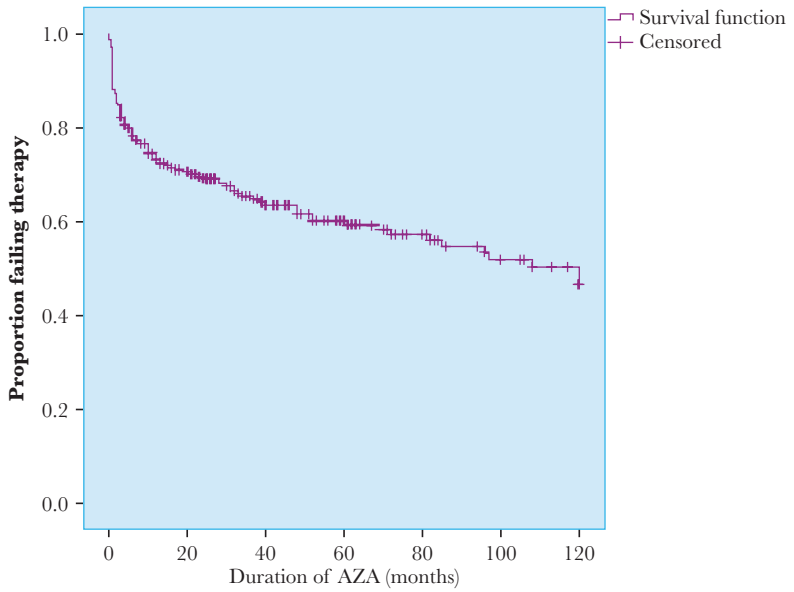

Figure 3. Kaplan-Meier survival plot showing proportion of patients with sustained clinical benefit at 120 months post-commencement of azathioprine (assessed at last point of follow-up).

to a biologic therapy and only one requiring colectomy. These data suggest that AZA is effective in sustaining clinical remission in the longer term. This is in keeping with other studies that have reported on the long-term efficacy of AZA in UC. In a study conducted by Fraser *et al.*,[19] 62% of patients still on AZA at 5 years remained in clinical remission. This increased to approximately 81% if those patients who experienced only short-term relapses were included. In a European multicenter study of 358 UC patients that reported on the glucocorticosteroid-sparing effect of long-term AZA therapy, there was a reduction in the median dose of prednisolone per month from 63 mg during the first 4 years of treatment to a median dose of 0 mg per month when extending AZA therapy beyond 4 years.[25]

Adverse events resulting in AZA cessation occurred in 29% of patients, which is in keeping with other published studies.[19,25–29]

More than 60% of these occurred within 4 months of AZA commencement, suggesting that AZA is likely to be well tolerated beyond this period. The commonest causes of AZA cessation at the last point of follow-up were myelotoxicity and hepatotoxicity, emphasizing the need for regular blood test monitoring in patients on long-term AZA treatment. Reassuringly, there were no cases of drug-related mortality and there was only one case of neutropenic sepsis. Azathioprine also appeared to be well tolerated in the long term, with only three of the adverse events resulting in AZA cessation occurring after 5 years of AZA therapy. Part of the explanation for the good tolerability of AZA we observed in our cohort may be the fact that we measured TPMT levels in >90% of our patients, and therefore the incidence of neutropenia was minimized. At the time of this study, our unit did not have access to thiopurine metabolite testing. Data suggest that the use of thiopurine improves efficacy and reduces thiopurine-induced toxicity.[30] The introduction of this test may therefore result in a more individualized approach to AZA therapy and could improve efficacy and reduce toxicity.

In conclusion, we established that AZA was a safe and effective treatment in a cohort of patients with UC, of whom three-quarters had become either dependent on or resistant to glucocorticosteroids, with <20% of all patients who commenced the drug progressing to hard endpoints such as the need for UC-related hospitalization, escalation of therapy to a biologic, or the need for colectomy at any point after commencement of AZA therapy. Moreover, AZA therapy for >5 years was well tolerated and resulted in long-term sustained clinical benefit, with low rates of treatment escalation and colectomy.

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None.

Conflict of interest statement

Dr. PJ Hamlin has served on advisory boards for Schering-Plough/MSD Pharmaceuticals. Dr. AC Ford has received speakers' fees from MSD and Shire Pharmaceuticals.

Statement of authorship

SA, TC and RS collated the data for the study. SA and RS analyzed the data and RS wrote the first draft of the manuscript. RS, PJH and ACF edited subsequent drafts. RS is guarantor and approved the final version of the manuscript.

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