RESEARCH

Effect of azathioprine intolerance on outcomes of inflammatory bowel disease: a cross-sectional study

Lennard Y W Lee, Anjum Syed Gardezi, Vidya Santharam, Jason Boyd, Sandro Lanzon-Miller

Department of Gastroenterology, Milton Keynes NHS Foundation Trust, Standing Way, Milton Keynes, UK

Correspondence to

Dr Lennard Lee, Milton Keynes NHS Foundation Trust, Standing Way, Milton Keynes MK6 5LD, UK; lennardylwlee@gmail.com

Received 20 May 2013

Revised 29 July 2013

Accepted 30 July 2013

Published Online First

20 August 2013

ABSTRACT

Background Azathioprine is well established for the maintenance of remission in patients with inflammatory bowel disease (IBD). However, a significant proportion of patients are intolerant to azathioprine. It is not clear if intolerance of azathioprine is a marker of poor prognosis for patients who will have a more aggressive disease or be more likely to require surgery.

Objective To determine if intolerance to azathioprine is a marker of poor prognosis, indicating patients who have a more aggressive disease course, and to analyse the risk factors and causes of intolerance.

Methods A cross-sectional study using the Milton Keynes Hospital IBD database was performed to compare azathioprine-intolerant and azathioprine-tolerant patients.

Results Two hundred and thirty-nine patients met the inclusion criteria comprising 141 patients with Crohn's disease (CD) and 98 patients with ulcerative colitis (UC). Overall, 28.0% of patients were intolerant to azathioprine. Risk factors for intolerance were female sex and age 50–70 years. Common reasons for intolerance were nausea and vomiting (34.3%), deranged liver function tests (28.4%) and headaches (11.9%). In patients with UC, there was no statistical difference in the disease activity scores between those who were azathioprine intolerant versus tolerant. In patients with CD, azathioprine intolerance was associated with significantly worse disease activity; 25% fewer patients were in clinical remission and 20% more had moderate/severe disease. Rates of surgery were similar between the groups for both UC/CD.

Conclusions We conclude that azathioprine intolerance acts as a surrogate marker for patients with CD who in future have poorer symptom control. Azathioprine intolerance marks out a group of patients with CD in whom increased vigilance of symptom control and early escalation of treatment is required.

INTRODUCTION

Azathioprine is an integral part of inflammatory bowel disease (IBD) management, with nearly 20% of patients with IBD using the drug in Europe.¹ Azathioprine induces gastrointestinal T cell apoptosis and decreases inflammation by conversion to a purine metabolite that binds to the GTPase Rac1.² It is effective at maintaining remission in both Crohn's disease (CD) and ulcerative colitis (UC).^{3 4}

However, nearly 30% of patients prescribed azathioprine have to stop treatment owing to adverse side effects or non-response.⁵ This variation in outcomes and adverse side effects may be partly explained by the enzyme thiopurine methyltransferase (TPMT), which is responsible for the breakdown of the drug, and patients with low TPMT levels are particularly prone to myelosuppression.⁵ Nevertheless, despite routine testing for TPMT, azathioprine intolerance is common.

A number of alternative treatments can be used to maintain remission in patients with IBD who are intolerant to azathioprine. These include methotrexate, mercaptopurine, thioguanine and anti-tumour necrosis factor (anti-TNF) treatments. However, the disease burden of patients who are intolerant to azathioprine has yet to be quantified.

In this study, we present a detailed description of the reasons for azathioprine intolerance and associated risk factors. We then analyse the disease outcomes for this cohort to determine if intolerance to azathioprine is a marker of poor prognosis, indicating patients who have a more aggressive disease course. By clarifying the disease burden we hope it will promote increased surveillance, discussion and research into this cohort of patients.

To cite: Lee LYW, Gardezi AS, Santharam V, et al. *Frontline Gastroenterology* 2014;**5**: 40–43.

METHODS

Study population

Patients were identified using the IBD database at a UK district general hospital. Inclusion criteria included patients older than 18 years, receiving active gastroenterology follow-up (defined as at least one attendance at the clinic within the past 12 months) and were using azathioprine or had previously stopped azathioprine treatment owing to adverse side effects.

Study design

The study was a single site, cross-sectional study.

Azathioprine intolerance

All doses of azathioprine were calculated according to the patient TPMT levels; patients with normal enzyme activity were given 2–2.5 mg/kg/day, patients with low enzyme activity were given 1–1.25 mg/kg/day. Patients were defined as being intolerant if they experienced adverse effects that led to the permanent discontinuation of the drug. Intolerance to azathioprine was identified by a search of the IBD database and cross-checked with a concurrent manual search of patient case records to ensure all cases were identified and validated.

Patient outcomes

A cross-sectional analysis of patient disease activity and outcomes was performed. Disease activity scores for patients with CD were based on the Harvey Bradshaw Index, ranging from <5 (clinical remission) to >16 (severe disease). Disease activity scores for patients with UC were based on the Montreal Classification, ranging from S0 (clinical remission) to S3 (severe disease). Disease activity indices were gathered from a manual search of the patient case records and were based on the last hospital episode. Steroid dependence was defined as the inability to taper glucocorticoids to <10 mg/day within 3 months of starting steroids, without recurrent disease, or if relapse occurred within 3 months of stopping glucocorticoids. Extensive disease was defined as the last colonoscopy showing pancolitis. Details of surgery, presence of fistula/strictures and use of monoclonal antibodies were recorded.

Statistical design and analysis

Statistical analysis was performed using SPSS V.20 (SPSS Inc, Chicago, Illinois, USA). A χ^2 test was performed to compare outcomes for azathioprine-intolerant and -tolerant patients with IBD. A log-rank test was performed to compare rates of surgery for azathioprine-intolerant and -tolerant patients. Statistical significance was taken at $p < 0.05$.

RESULTS

Two hundred and thirty-nine patients met the inclusion criteria for this study and consisted of 141 patients

Table 1 Reasons for azathioprine intolerance from CD/UC cohort

Reason for intolerance	Number of patients (n=67)
Nausea + vomiting	23 (34.3)
Deranged liver function tests	19 (28.4)
Headaches	8 (11.9)
Dermatological side effects	5 (7.5)
Leucopenia	4 (6.0)
Arthralgia	3 (4.5)
Influenza symptoms	2 (3.0)
Infection	1 (1.5)
Depression	1 (1.5)
No information	1 (1.5)

Results are shown as number (%).

CD, Crohn's disease; UC, ulcerative colitis.

with CD and 98 patients with UC. The median age of this cohort was 38 years and 32.5% of patients were male. The mean follow-up was 13.5 years.

Azathioprine-intolerant cohort

Overall, 28.0% of patients were intolerant of azathioprine (n=67). The median age of patients was 47 years and 26.9% of patients were male. The most common reason for intolerance was nausea and vomiting (34.3%), deranged liver function tests (LFTs, 28.4%) and headaches (11.9%) (table 1). After the unsuccessful introduction of azathioprine, this cohort of patients was subsequently treated with infliximab (20.9%), mercaptopurine (10.4%), methotrexate (6.0%) and adalimumab (4.5%) (table 2).

Table 2 Patients with azathioprine intolerance: demographics and subsequent treatment

Demographics/treatment	Azathioprine intolerant (n=67)
Sex	
Male	18 (26.9)
Age (years)	
<30	8 (11.9)
30–50	27 (40.3)
50–70	32 (47.8)
Concurrent 5-ASA drugs	33 (49.3)
Ethnicity	
Caucasian	65 (97.0)
Asian-Indian	2 (3.0)
Diagnosis	
Ulcerative colitis	32 (47.8)
Crohn's disease	35 (52.2)
Subsequent treatment	
Mercaptopurine	7 (10.4)
Methotrexate	4 (6.0)
Infliximab	14 (20.9)
Adalimumab	3 (4.5)

Results are shown as number (%). 5-ASA, 5-aminosalicylic acid.

Table 3 Outcomes of patients with CD according to tolerance to azathioprine

CD cohort	Azathioprine intolerant (n=35)	Azathioprine tolerant (n=106)	p Value
Patients with stricture/fistula	17 (48.6)	63 (59.4)	0.326
Requiring surgery	13 (37.1)	55 (51.9)	0.124
Extensive disease	3/30 (10)	11/92 (12.0)	1.000
Disease activity:			
Remission—HBI <5	19/34 (55.9)	76/96 (79.2)	0.027*
Mild disease—HBI 5–7	7/34 (20.6)	17/96 (17.7)	0.798
Moderate disease—HBI 8–16	8/34 (23.5)	3/96 (3.1)	0.001*
Severe disease—HBI >16	0/34 (0)	0/96 (0)	1.000
Steroid dependent	7 (20.0)	2 (1.9)	<0.001*
Monoclonal antibody	9 (25.7)	13 (12.3)	0.065

Results are shown as number (%).

*Statistically significant.

CD, Crohn's disease; HBI, Harvey Bradshaw Index.

Crohn's disease cohort

Of the 141 patients with CD, 35 (24.8%) were intolerant to azathioprine. Azathioprine was not tolerated owing to gastrointestinal side effects in 53.6% (nausea/vomiting), headaches in 17.9%, deranged LFTs in 17.9%

Within the CD cohort, 68 (48.2%) patients required surgery during the follow-up period. Rates of surgery did not differ between patients who were azathioprine intolerant or tolerant. The median time from diagnosis to time of surgery was 3.9 years in those who were azathioprine tolerant and 7.4 years in those who were azathioprine intolerant. There was a significant difference between the azathioprine-intolerant and -tolerant cohorts in the number who were steroid dependent ($p<0.001$). The Harvey Bradshaw Index was statistically different between the cohorts; nearly 25% fewer patients were in clinical remission and 20% more had moderate/severe disease in the azathioprine-intolerant cohort ($p<0.001$) (table 3).

Ulcerative colitis cohort

Of the 98 patients with UC, 32 (32.7%) were intolerant to azathioprine. Azathioprine was not tolerated owing to deranged LFTs in 43.3%, gastrointestinal symptoms of nausea/vomiting in 23.3%, cutaneous side effects in 10.0%, migraines in 6.7% and infections in 3.3%.

In the UC cohort, 17 (17.3%) patients required surgery during the follow-up period. Rates of surgery were not different between patients who were azathioprine intolerant or tolerant. The median time from diagnosis to time of surgery was 4.4 years in those who were azathioprine tolerant and 2.4 years in those who were azathioprine intolerant. These differences were not statistically significant. More patients in the azathioprine-intolerant cohort were steroid dependent ($p<0.001$). However, azathioprine intolerance did not have a statistically significant effect on disease activity (table 4).

Predictors of azathioprine intolerance

An analysis of the baseline demographics of azathioprine-intolerant patients was performed. Patients intolerant to azathioprine were significantly more likely to be female (relative risk (RR)=1.56, $p=0.038$) and aged 50–70 years (RR=1.61, $p=0.010$).

DISCUSSION AND CONCLUSIONS

Within the past two decades there have been rapid changes in the management of IBD. The traditional tiered 'step-up' approach in treatment starting with steroids has now been replaced by the use of time-critical structured approach, the 'accelerated step-up' approach and for some patients with a severe phenotype, 'top-down treatment' starting with anti-TNF agents.

Table 4 Outcomes of patients with UC according to tolerance to Azathioprine

UC cohort	Azathioprine intolerant (n=32)	Azathioprine tolerant (n=66)	p Value
Requiring surgery	6 (18.8)	11 (16.7)	0.775
Extensive disease	9 (28.1)	24 (36.4)	0.498
S2/S3 disease	11 (34.4)	19 (28.8)	0.643
S0/S1 disease	21 (65.6)	47 (71.2)	0.643
S0 disease—remission	12 (37.5)	30 (45.5)	0.518
Steroid dependent	9 (28.1)	0 (0.0)	>0.001*

Results are shown as number (%).

*Statistically significant.

UC, ulcerative colitis.

However, each of the drugs in the treatment ladder is associated with risks and potential significant adverse side events. Azathioprine remains an integral part of IBD management and yet intolerance is common. The evidence for alternatives remains weaker. Some groups advocate escalation straight to anti-TNF agents, others using a personalised pharmacometabonomics approach using allopurinol,⁶ others thioguanine^{7–8} and there is limited evidence for methotrexate.^{9–10} However, many of these approaches lack large-scale studies and long-term safety profiles and patients and clinicians are often wary to escalate to these treatments.

Investigators have previously reported thiopurine intolerance of 25–40%.^{11–12} Our experience suggests this percentage is 28% with the most common reasons being nausea/vomiting, deranged LFTs and headaches. The UC cohort had a much higher incidence of deranged LFTs than the CD cohort and this has not been previously noted. Previous authors have reported that smoking is a risk factor for azathioprine intolerance,¹³ and although these data were not collected and we cannot comment on this finding, this study indicates that female sex and age 50–70 years are additional further risk factors.

Azathioprine-intolerant patients with CD were not at greater risks of developing fistulas/strictures or require surgery, and similarly, azathioprine-intolerant patients with UC were not at increased risks of requiring colectomy. This similar surgery risk was unexpected, but not entirely unsurprising as patients with azathioprine intolerance were often escalated to anti-TNF agents and there is evidence for early azathioprine use only as a disease-modifying drug.¹⁴ However, azathioprine intolerance in patients with CD was associated with significantly poorer symptom control with fewer patients in remission and more with moderate–severe active disease. This effect was less marked in patients in UC and probably not statistically significant owing to the small sample size.

The study has some limitations. It reflects the management of patients in a single UK hospital that uses an ‘accelerated step-up’ strategy. Furthermore, only one in seven of the patients with CD was receiving infliximab and this lower usage reflects the limited anti-TNF licence in the UK. The generalisation of our findings outside this setting is not clear. Nevertheless, the strengths of this study derive from robust long-term follow-up of a cohort of patients from a database, allowing in-depth analysis of outcomes and causes of intolerance. Further research into the causes and risk factors for azathioprine intolerance is required and the results of the PRED4 study will help to determine underlying causes.

In conclusion, azathioprine intolerance acts as a surrogate marker for patients with CD who may in future have poorer symptom control. The most common reasons for intolerance are nausea/vomiting,

deranged LFTs and headaches. Female sex and an older age are associated with intolerance and initiating the drug in this cohort requires caution. Azathioprine intolerance marks out a cohort of patients in whom increased vigilance of symptom control is warranted and early escalation of treatment required.

Contributors LYWL: wrote the manuscript and is guarantor of the article. ASG, VS and JBD: gathered the data and carried out the analysis. SL-M: senior author. All authors approved the final version of this manuscript.

Competing interests None.

Provenance and peer review Not commissioned; externally peer reviewed.

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