Characteristics of azathioprine use and cessation in a longitudinal lupus cohort

Lucy Croyle, Alberta Hoi, Eric F Morand

ABSTRACT

Objective: Guidelines for azathioprine (AZA) use in systemic lupus erythematosus (SLE), including indications for initiation and cessation, are lacking. Clinical decision-making could be improved if reasons for cessation of AZA treatment were standardised.

Methods: We determined the characteristics of AZA use in a cohort of patients with SLE and evaluated reasons for AZA cessation. Patients with SLE in a single centre had longitudinal recording of disease activity (Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI)-2k), laboratory investigations and treatment from 2007 to 2012.

Results: Of 183 patients studied, 67 used AZA on at least one occasion. There was no significant difference between AZA users and non-users in age or American College of Rheumatology criteria. Compared with those not treated with AZA, patients treated with AZA had higher disease activity (time-adjusted mean SLEDAI 5.2±0.3 vs 3.8±0.3, p=0.0028) and damage (Systemic Lupus International Collaborating Clinics (SLICC)-SDI 1.6±0.3 vs 1.2±0.1, p=0.0445), and were more likely to have a positive dsDNA (p=0.0001). AZA therapy was ceased in 30/67 (45%) patients. The predominant reasons for cessation were treatment de-escalation 14 (47%), treatment failure 12 (40%) and toxicity 3 (10%). AZA therapy was ceased in 30/67 (45%) patients. The predominant reasons for cessation were treatment de-escalation 14 (47%), treatment failure 12 (40%) and toxicity 3 (10%). AZA was switched to mycophenolate mofetil (MMF) in 9/12 (75%) of treatment failures, and this choice was strongly associated with active lupus nephritis.

Conclusions: AZA toxicity was uncommon, and many patients ceased therapy in the context of treatment de-escalation. However, the frequent development of active lupus nephritis requiring MMF suggests the need to distinguish refractoriness, under-treatment and non-adherence to AZA in patients with SLE. These findings suggest that future studies of AZA metabolite measurement could prove valuable in the management of SLE.

INTRODUCTION

Azathioprine (AZA) is a valuable immunosuppressant for the treatment of multiple manifestations of systemic lupus erythematosus (SLE). Following the MAINTAIN trial and ALMS study, mycophenolate mofetil (MMF) has largely usurped AZA as the therapy of choice in lupus nephritis, for both inducing remission and as maintenance therapy. However, in a patient population consisting predominantly of women in their child-bearing years, AZA is one of only a few medications deemed safe for use during pregnancy and it remains widely used. Pre-therapy measurement of thiopurine methyltransferase (TPMT) enzyme levels is accepted practice and provides an indication of treatment adher-ence. However, the TPMT test does not universally implement TPMT measurement in the management of AZA therapy.

Evidence in autoimmune hepatitis and inflammatory bowel disease (IBD) designates a target range for AZA metabolites that correlates with avoidance of serious toxicity, attaining and sustaining remission, as well as providing an indication of treatment adherence. This has not been applied in SLE. For patients with active SLE despite AZA, appropriate designation as non-compliant, treatment-refractory or undertreated could improve clinical decision-making as has been shown most clearly in IBD.

Given the evolving prospects for improving clinical decision-making via therapeutic drug monitoring of AZA, we sought to evaluate patterns of AZA cessation in an SLE cohort, to determine whether reasons for cessation are

KEY MESSAGES

- Azathioprine is a commonly used immunosuppressant for all manifestations of SLE, however indications for its use and cessation are not standardized.
- We describe the use and cessation of AZA in our SLE cohort, with 50% of cessation due to treatment failure or toxicity and the remainder undergoing de-escalation.
- Distinguishing true treatment refractoriness from undertreatment or non-compliance, and toxicity from disease activity may be enhanced with use of AZA metabolite measures.
of AZA in routine practice supported the potential utility of metabolite monitoring. We found that a significant proportion of patients ceased AZA therapy due to poor control of disease, implying that designation of the cause of therapeutic failure through metabolite monitoring could frequently be of benefit.

METHODS

We performed a retrospective study of longitudinal data, acquired prospectively in a single centre. As previously described,17–19 all patients with SLE (≥4 American College of Rheumatology (ACR) criteria20) attending the Lupus Clinic at Monash Medical Centre, Melbourne, Australia, were invited to be included in a database, approved by the Human Research Ethics committee of Monash Health. After written informed consent, baseline demographic and clinical data were collected on all patients during routine visits to the SLE clinic by the attending physician using standard proformas. Recording of disease activity (hybrid SELENA-Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2k))21, laboratory investigations (serum complement, anti-dsDNA antibodies, full blood count, electrolytes, liver function tests, proteinuria (urine protein: creatinine ratio) and urine microscopy) and treatment details are completed at each visit as previously described.17–19 Disease-related damage is recorded annually using the Systemic Lupus International Collaborating Clinics (SLICC)-SDI22 and time-adjusted mean SLEDAI (AMS), a measure of mean disease activity adjusted for the period of observation, calculated.

All patients included in the database between January 2007 and November 2012 were assessed for inclusion; data on medication use prior to enrolment in the database were not available. Inclusion criteria for this study were at least one complete set of visit data during the study period. Patients using AZA at any time during the period of observation were identified and details of disease activity and medication use extracted. AZA cessation was defined when documented use of AZA was terminated during the period of observation. Medications used prior to, during and following AZA use were documented, as were prednisolone dose changes at time of AZA cessation. Reasons for AZA cessation were designated as toxicity, treatment failure or de-escalation. Toxicity was defined when abnormal liver function or haematological parameters were present at the time of cessation. Treatment failure was defined where patients ceasing AZA underwent escalation of corticosteroid dose or institution of replacement immunosuppressive therapy. De-escalation was defined when AZA was ceased but no escalation in glucocorticoids or treatment replacement for AZA was instituted, assuming the definitions of toxicity or treatment failure were not met. Disease activity at the time of AZA cessation was evaluated to verify the presence of treatment failure.

Attainment of the recently described lupus low-disease activity state (LLDAS)23 at AZA cessation was assessed.

For comparison of means, continuous data were analysed using Student’s t tests, while discontinuous data were analysed using Mann–Whitney rank tests. For comparisons of prevalence and calculation of ORs, Fisher’s exact test was used. All statistical analyses were completed using GraphPad Prism Software V6.0.

RESULTS

A total of 183 patients were studied. Characteristics of the study population are shown in table 1. Of 183 patients studied, 67 (37%) used AZA on at least one occasion during the study period. Among patients who had used AZA, the median (range) dose of AZA used across the period of observation was 95 mg/day (50–150 mg/day).

We next compared clinical characteristics between patients who used AZA and those who did not. As shown in table 2, there was no significant difference in age or number of ACR criteria fulfilled between patients using AZA and those not.

Patients using AZA had a significantly longer total period of observation, and a greater number of visits recorded than patients not using AZA (table 2). Patients who were treated with AZA at any time during the period of observation had significantly higher AMS, indicating higher disease activity across the period of observation (p=0.0028, table 2). Ethnicity differed significantly, in that patients of Caucasian ethnicity were significantly over-represented among patients using AZA (table 2). No
significant difference in cumulative damage, as measured using SLICC-SDI at the last assessment, was observed (table 2). Patients using AZA were more likely to have anti-dsDNA antibodies (p=0.0001) and were exposed to a significantly higher adjusted mean glucocorticoid dose (p=0.0386, table 2), than patients not exposed to AZA. Concomitant treatment with hydroxychloroquine (HCQ) occurred in 65/67 (97%) of the AZA cohort, and 104/116 (89.7%) of non-AZA cohort (NS).

Of the 67 AZA users, 29 commenced AZA during the period of observation, allowing us a view of preceding medications and disease trajectory. Of those starting AZA during the period of observation, 24/29 had used preceding lupus medications including MMF (6 patients) methotrexate (MTX) (4), cyclophosphamide (2), rituximab (1), HCQ (22) and prednisolone (6 patients) methotrexate (4), cyclophosphamide (2), rituximab (1), HCQ (22) and prednisolone (6 patients) methotrexate (4), cyclophosphamide (2), rituximab (1), HCQ (22) and prednisolone (6 patients) methotrexate (4), cyclophosphamide (2), rituximab (1), HCQ (22) and prednisolone (6 patients). Among the patients who switched from AZA to MMF, the median dose was 100 mg/day (range 53–143); a median (range) dose of 1.521 mg/kg/day for AZA-MMF patients compared with those who switched to other treatments (AZA-other) (table 3). None of the patients who ceased AZA due to treatment failure met criteria for LLDAS.

On the basis that MMF is most frequently used for the treatment of lupus nephritis, we analysed renal disease activity using the renal domains of SLEDAI (urinary casts, proteinuria, haematuria, pyuria).24 25 AZA-MMF patients had significantly higher renal SLEDAI than AZA-other patients (p=0.0214, table 3). Data on histological class of lupus nephritis are stored in our database; however, only patients with Class III/IV/V lupus nephritis qualify for MMF treatment in our centre. Contingency analysis revealed that the relative risk of active renal disease in AZA-MMF patients compared with AZA-other patients was 4.6 (95% CI 1.1 to 18.4, p=0.019). This suggests that active lupus nephritis developing during AZA therapy was driving treatment escalation to MMF. Among the patients who switched from AZA to MMF, the median dose was 100 mg/day (range 53–143); a median (range) dose of 1.521 mg/kg/day (0.839–2.123). This was not different from the median (range) 1.527 (0.547–2.50) mg/kg/day in the overall population on AZA. In contrast, lupus nephritis was not the major lesion in the 3/12 treatment failure patients whose therapy was changed to immunosuppressive treatment other than MMF.

Toxicity, in the form of leukocytopenia, was the reason for cessation in three patients (10% of patients ceasing AZA). Of the three neutropenic patients, a nadir of 1.3×10⁹ leucocytes/L was observed in a patient with

| Table 2 Characteristics of azathioprine (AZA) users versus non-AZA users |
|-----------------|-----------------|-----------------|
| **N** | 67 | 116 |
| Age (year, mean±SEM) | 43±2 | 45±1 |
| Ethnicity (n; %) (Asian:Caucasian:other*) | 29:32:6 | 61:22:33 |
| ACR criteria (median (range)) | 5 (4–9) | 5 (4–9) |
| Duration SLE | 10.09±0.8840 | 9.776±0.7368 |
| Visits observed (n, median (IQR)) | 18 (9–26) | 9 (4–16) |
| Period observed (days, median (IQR)) | 1316 (798–1701) | 889 (369–1545) |
| Anti-dsDNA-positive | 54 (80.6%) | 77 (67.5%) |
| AMS (mean±SEM) | 60 (89.5%) | 79 (68.1%) |
| Hypocomplementemia (n (%)) | 65 (97%) | 73 (63%) |
| SDI (median (range)) | 1 (0–12) | 1 (0–7) |
| Corticosteroid use | 65 (97%) | 73 (63%) |
| Adjusted mean prednisone dose (mg/day, mean±SEM) | 7.6±0.66 | 5.6±0.62 |
| Hydroxychloroquine use | 65/67 (97%) | 104/116 (89.7%) |

Data refer to period of observation recorded.
*Other—those identifying as ‘other’ or declining to be identified ethnically.
ACR, American College of Rheumatology; AMS, (time) adjusted mean SLEDAI; SLE, systemic lupus erythematosus; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index.
likely lupus-induced neutropenia, evidenced by further reduction to 0.48×10⁹ leucocytes/L 14 months post cessation of AZA, with no other cytopenia-inducing medications. The other two patients had neutrophil nadirs of 0.97 and 1.78×10⁹ leucocytes/L, both of which improved over 1–4 months with cessation of AZA and use of prednisolone, consistent with AZA-mediated bone marrow suppression.

DISCUSSION

In SLE, AZA is generally prescribed for active non-renal disease, using weight-based dosing with varying suggested adjustments for renal impairment.²⁶,²⁷ As control of disease activity is a key goal in SLE,²⁸,²⁹ the presence of active disease despite AZA therapy may result in the presumption of inefficacy and switching of AZA to another therapy. Dose escalation is an alternative to switching, but the frequency of dose-limiting AZA toxicity in patients with SLE is not well described. An individualised metabolite monitoring-based approach to AZA therapy in SLE has been suggested as a way to distinguish disease activity due to underexposure or non-adherence as opposed to medication refractoriness, and potentially distinguish AZA toxicity from active SLE as a cause of leucopenia.³⁰ However, the frequency of these differing outcomes in AZA-treated patients with SLE is poorly understood, and hence the potential benefit of the application of AZA metabolite monitoring as a standard of care in SLE is unclear. We therefore undertook a study of AZA use in a longitudinally followed SLE cohort, focusing on reasons for treatment cessation, to determine whether reasons for AZA termination in routine practice supported the potential use of monitoring.

First, we observed that AZA use was common. In this cohort, AZA was prescribed in patients with more severe disease, as suggested by higher disease activity, anti-dsDNA positivity and use of corticosteroids. An average AMS of >5 indicates inadequate overall disease control in AZA-treated patients. This finding alone suggests the need for improved use of AZA in SLE, potentially using AZA metabolite monitoring to optimise dosing.

Second, a significant proportion of patients ceased AZA therapy during the period of observation. The most common reason for AZA cessation was treatment de-escalation, followed by treatment failure. In contrast, cessation of AZA due to toxicity was uncommon. Nearly a quarter of all patients with SLE treated with AZA ceased therapy in a setting of treatment de-escalation. Long-term continuation of HCQ is now commonplace,³¹ but there is a lack of data regarding the optimal duration of other therapies, especially in the setting of low-disease activity.³ Interestingly, not all patients who ceased AZA for treatment de-escalation had ‘low-disease activity’ according to a definition proposed recently.²³ The current study was not designed to assess outcomes after treatment de-escalation, but it would be useful in future studies to investigate outcomes subsequent to de-escalation of AZA therapy in patients with stable disease.

Outside the setting of clinical trials, treatment cessation decisions are based on a myriad of factors, and while many are captured in longitudinal cohort databases such as that studied here, others, including the impact of individual patient preference, and subjective measures of intolerability (nausea) are not.³² This highlights a limitation of the current study, in that the data were originally collected for the purpose of analysing longitudinal disease activity³³ and were retrospectively analysed. Further limitations include the potential bias arising from studying a single-centre cohort. Finally, compliance and appropriate documentation cannot be assessed in this format.

The second most frequent reason for AZA cessation was treatment failure, defined as an escalation of therapy in the setting of active disease. There is increasing acceptance of the use of MMF for the treatment of lupus nephritis,⁸ and active nephritis was the dominant clinical feature in patients changing from AZA to MMF in the current study. The observation that 9 of 67

<table>
<thead>
<tr>
<th>Table 3 Reasons for AZA cessation</th>
<th>Total</th>
<th>Cessation</th>
<th>No cessation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>67</td>
<td>30</td>
<td>37</td>
</tr>
<tr>
<td>De-escalation</td>
<td></td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Toxicity</td>
<td></td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Treatment failure</td>
<td></td>
<td>12</td>
<td></td>
</tr>
<tr>
<td></td>
<td>AZA-MMF*</td>
<td>AZA-other†</td>
<td>p Value</td>
</tr>
<tr>
<td>(n, (%))</td>
<td>9 (75%)</td>
<td>3 (25%)</td>
<td>NS</td>
</tr>
<tr>
<td>SLEDAI (mean±SEM)</td>
<td>10.14±2.45</td>
<td>5.59±1.2</td>
<td>0.0214</td>
</tr>
<tr>
<td>Renal SLEDAI (mean±SEM)</td>
<td>4.44±1.0</td>
<td>1.52±0.65</td>
<td></td>
</tr>
</tbody>
</table>

*AZA-MMF: switched from AZA to MMF.
†AZA-other: switched from AZA to treatment other than MMF.
AZA, azathioprine; MMF, mycophenolate mofetil; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index.

AZA-treated patients developed active lupus nephritis requiring escalation to MMF suggests these cases were regarded by the treating physician as AZA-refractory. While AZA dosing recommendations vary according to disease manifestations of SLE, a maximum dose of 2 mg/kg is advised as maintenance therapy for lupus nephritis. The median dose in AZA-MMF patients was 1.5 mg/kg/day, and only two patients who transitioned to MMF in the setting of active renal disease were receiving a dose ≥2 mg/kg, suggesting these patients may have been undertreated.

We propose that distinguishing between true treatment refractoriness, as opposed to under-dosing and non-adherence, and between toxicity and lupus-related leukopenia, would be possible through the measurement of AZA metabolites. Half of all patients on AZA in this study ceased treatment due to presumed inefficacy or toxicity, suggesting that as many as half of all patients with SLE treated with AZA could benefit from metabolite monitoring. One study in IBD using an AZA metabolite-based dosing algorithm found 24% of patients avoided inappropriate dose escalation, and 87% of patients achieved improved clinical outcomes. The application of such an approach in SLE has been suggested, but application of such an approach is limited by the fact that an empirically defined therapeutic range for AZA metabolites in SLE is lacking. Two small studies in mixed cohorts of connective tissue disease patients confirmed high inter-individual variation of metabolite levels, and poor correlation of metabolite levels with weight-adjusted doses. A 6-month dose escalation study of 50 patients with SLE identified a target level of AZA metabolites that correlated with efficacy. Doses required to achieve this were approximately 3 mg/kg/day, higher than current dosing guidelines for lupus nephritis maintenance and similar to maximum dosing recommendations for other autoimmune manifestations. This suggests that inappropriate designation of patients as AZA-refractory may be common in SLE.

Pre-drug TPMT testing was not routinely undertaken in our cohort. It remains a matter of debate whether genotype or phenotype (TPMT enzyme testing) is superior in our cohort. It remains a matter of debate whether genotype or phenotype (TPMT enzyme testing) is superior in our cohort. It remains a matter of debate whether genotype or phenotype (TPMT enzyme testing) is superior in our cohort. It remains a matter of debate whether genotype or phenotype (TPMT enzyme testing) is superior in our cohort.

In conclusion, AZA was a frequently used immunosuppressant in this SLE cohort, but was withdrawn in a high proportion of cases. AZA cessation for toxicity was infrequent, while development of active lupus, including nephritis, requiring treatment escalation to mycophenolate was much more frequent. This suggests that breakthrough disease activity, implying AZA-refractoriness, undertreatment or non-adherence, greatly exceeds AZA toxicity as a management issue in SLE. In addition, when combined, the potential for AZA metabolite monitoring to influence physician decisions was present in half of all patients with SLE treated with AZA. We conclude that knowledge of AZA metabolite concentrations could potentially aid decision-making as part of the standard of care in SLE, for which prospective studies of AZA metabolite levels in SLE and strategy trials of recently proposed metabolite-based dosing algorithms are required. The outcomes of such research could include more stringent guidelines for the use of AZA in SLE, potentially resulting in highly cost-reducing interventions in disease activity and prevention of treatment escalation.

Acknowledgements Susan Morton, Research Nurse, Monash Medical Centre, Melbourne, Australia.

Contributors All authors have contributed to the article, with major writing being done by LC, with assistance in the form of editing, format and statistics from EFM, and editing and database assistance from AH.

Funding Australian Rheumatology Association—the SA LSS Support Group funded by Arthritis South Australia.

Competing interests None declared.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement There are no data sharing instructions or arrangements with no further unpublished data.

Open Access This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

REFERENCES


Characteristics of azathioprine use and cessation in a longitudinal lupus cohort

Lucy Croyle, Alberta Hoi and Eric F Morand

*Lupus Sci Med* 2015 2:
doi: 10.1136/lupus-2015-000105

Updated information and services can be found at:
http://lupus.bmj.com/content/2/1/e000105

These include:

**References**
This article cites 36 articles, 3 of which you can access for free at:
http://lupus.bmj.com/content/2/1/e000105#ref-list-1

**Open Access**
This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

**Email alerting service**
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

**Topic Collections**
Articles on similar topics can be found in the following collections

Epidemiology and Outcomes (29)

**Notes**

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/