CASE REPORT

Azathioprine as a steroid sparing agent in leprosy Type 2 reactions: Report of nine cases

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Introduction

Glucocorticosteroids (GCS) are the main therapeutic agent used to treat leprosy reactions. Some patients have prolonged reactions and require prolonged therapy with GCS.1,2 Corticosteroid-sparing agents have been used especially in patients with rheumatological diseases to reduce the GCS doses required to control the disease, or as an alternative to GCS, and to reduce side effects. The literature contains few experiences in the use of such GCS sparing agents in leprosy reactions. After methotrexate (whose use is widespread in psoriasis), azathioprine is the immunosuppressant most widely used by dermatologists because of its immunosuppressive effect, which is superior to methotrexate, has less serious side effects than cyclosporine, and a lower cost than that of mycophenolate, tracolimus and sirolimus. These factors guided our predilection for the use of azathioprine over other immunosuppressants since we started using it in 1996, yet there was no publication about its use in leprosy reactions.

From 2003 onwards articles began to emerge on the use of azathioprine in leprosy reactions. In the treatment of Type 1 reactions, when followed by prednisolone, it has been found to provide results comparable to those with prednisolone alone,3 thus possibly
providing a steroid-sparing regimen in the treatment of this reaction. Azathioprine alone has not been assessed in the treatment of Type 2 reactions, but has been reported to be useful in combination with prednisolone in three patients in the management of intractable Type 2 reactions that do not respond well to prednisolone alone, and associated to prednisolone and clofazimine in one patient. In a report, azathioprine was given after the acute episode in an attempt to prevent recurrences. We report the use of azathioprine in nine patients with severe Erythema nodosum leprosum (ENL). This is a retrospective notes-based study of patients attending the leprosy clinic of Antonio Pedro University Hospital at Universidade Federal Fluminense, Rio de Janeiro.

**Materials and Methods**

The study was conducted from 1996 to 2010. Leprosy patients (during or after multidrug therapy) needing corticosteroid therapy for ENL were selected from amongst those attending the dermatology clinic, and considered for the addition of a steroid-sparing agent. Any patients with anaemia, liver disease, renal disease, cardiac disease, cognitive deficit, or who were not able to attend the clinic for monitoring the blood count and liver tests were excluded. Patients were managed as outpatients and admitted only if their reactions were severe. ENL was defined as recurrent crops of painful erythematous noduloplaque lesions accompanied by fever, malaise and lymphadenopathy. Neuritis was defined as spontaneous nerve pain, tenderness or nerve function impairment (NFI) assessed by the usual clinical examinations of voluntary muscle testing, and sensory testing with a monofilament.

Amongst the nine patients, in six (1, 2, 3, 4, 5 and 6) azathioprine was introduced after completing multidrug therapy (MDT) and in three, (7, 8 and 9) azathioprine was introduced before the completion of MDT. Azathioprine was used at 2–3 mg/kg/d in association with GCS for all cases. The dose of prednisone was gradually reduced (approximately 10 mg per 15 days) from 4 weeks after the introduction of azathioprine. In the first month, monitoring of the blood count and liver enzyme levels was performed weekly; in the second month, biweekly and then monthly until the end of treatment. The outcome measure was the absence of skin lesions and no additional NFI. The appearance of new skin lesions or worsening of neurological functions precipitated a return to the previous dose of prednisone.

**Results**

Of the nine patients, one had to discontinue the azathioprine treatment due to drug induced hepatitis (case 6). Of the remaining eight patients, azathioprine was added to treatment in the first reaction episode (patients 7, 8 and 9) due to the severity of the reaction. In five patients azathioprine was added after a few episodes (patients 1, 2, 3, 4 and 5). In these five patients the dose of prednisone was cut to half in 12 weeks. In two patients, (cases 2 and 3) prednisone was withdrawn by 8 and 4 months respectively. Another two patients (cases 1 and 5) obtained better control of reactions with lower frequency and severity of episodes at a low dose of prednisone. In one patient (case 4), the reduction in frequency and severity of episodes occurred only after 20 weeks. Patients who began treatment with azathioprine at the first reaction episode required a much shorter treatment with high doses of GCS than those who began azathioprine after initial ENL reactions.
### Table 1. Patients characteristics and reaction patterns before and after introduction of azathioprine

<table>
<thead>
<tr>
<th>Case</th>
<th>Age</th>
<th>Sex</th>
<th>Class</th>
<th>Reaction Type</th>
<th>Length of treatment with prednisone before azathioprine (in years)</th>
<th>Prednisone daily dose range before AZA</th>
<th>Total dose prednisone</th>
<th>Length of treatment with azathioprine in weeks</th>
<th>↓ 50% prednisone in 12 weeks</th>
<th>↓ frequency and severity of outbreaks</th>
<th>Adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>23</td>
<td>F</td>
<td>BL</td>
<td>ENL + neuritis</td>
<td>2</td>
<td>50 to 100 mg</td>
<td>36 500 mg</td>
<td>86</td>
<td>Yes</td>
<td>Since start of treatment</td>
<td>–</td>
</tr>
<tr>
<td>2</td>
<td>20</td>
<td>F</td>
<td>L</td>
<td>ENL + neuritis</td>
<td>2</td>
<td>30 to 100 mg</td>
<td>21 900 mg</td>
<td>66</td>
<td>Yes</td>
<td>Since start of treatment</td>
<td>–</td>
</tr>
<tr>
<td>3</td>
<td>27</td>
<td>F</td>
<td>BL</td>
<td>ENL + neuritis</td>
<td>8</td>
<td>40 to 100 mg</td>
<td>116 800 mg</td>
<td>112</td>
<td>Yes</td>
<td>Since start of treatment</td>
<td>–</td>
</tr>
<tr>
<td>4</td>
<td>28</td>
<td>M</td>
<td>BL</td>
<td>ENL + neuritis</td>
<td>3</td>
<td>30 to 100 mg</td>
<td>38 325 mg</td>
<td>33</td>
<td>Yes</td>
<td>After 20th week</td>
<td>–</td>
</tr>
<tr>
<td>5</td>
<td>30</td>
<td>M</td>
<td>L</td>
<td>ENL + neuritis</td>
<td>5</td>
<td>30 to 80 mg</td>
<td>73 000 mg</td>
<td>28</td>
<td>Yes</td>
<td>Since start of treatment</td>
<td>–</td>
</tr>
<tr>
<td>6</td>
<td>30</td>
<td>M</td>
<td>L</td>
<td>ENL</td>
<td>3</td>
<td>30 to 80 mg</td>
<td>38 300 mg</td>
<td>3</td>
<td>UnEvaluated</td>
<td>UnEvaluated</td>
<td>Hepatitis</td>
</tr>
<tr>
<td>7</td>
<td>26</td>
<td>M</td>
<td>BL</td>
<td>ENL + neuritis</td>
<td>–</td>
<td>–</td>
<td>10 000 mg</td>
<td>110</td>
<td>Yes</td>
<td>Since start of treatment</td>
<td>–</td>
</tr>
<tr>
<td>8</td>
<td>50</td>
<td>M</td>
<td>BL</td>
<td>ENL + neuritis</td>
<td>–</td>
<td>–</td>
<td>6075 mg</td>
<td>110</td>
<td>Yes</td>
<td>Since start of treatment</td>
<td>Thrombocytopenia</td>
</tr>
<tr>
<td>9</td>
<td>27</td>
<td>M</td>
<td>BL</td>
<td>ENL + neuritis</td>
<td>–</td>
<td>–</td>
<td>4650 mg</td>
<td>33</td>
<td>Yes</td>
<td>Since start of treatment</td>
<td>–</td>
</tr>
</tbody>
</table>
**Details of Cases**

Age, sex, clinical classification, type of reaction and the data presented above are summarised in Table 1.

**Case 1** – Had been receiving prednisone for 2 years, (1994 to 1996) for ENL during MDT; the lowest dose without reaction was 50 mg/d. Her reactions continued after completing azathioprine 100 mg/d, the reactions became less severe and less frequent, and she reached the dose of 5 mg/d by the end of the second year (1998). The total prednisone dose was 36,500 mg and she was given azathioprine for 86 weeks.

**Case 2** – Over 2 years suffering reactions during MDT, the lowest dose of prednisone achieved was 30 mg/d (1998 to 2000). After the introduction of azathioprine 100 mg/d, the dose of prednisone was lowered and withdrawn by 8 months. The total prednisone dose was 21,900 mg and azathioprine was used for 66 weeks.

**Case 3** – Had continuing ENL from 1999 till 2007. She was treated with methylprednisolone pulse therapy and took prednisone and thalidomide. In 2007 (7 years after completing MDT), she started azathioprine 100 mg/d and her ENL reduced in severity and frequency. Her azathioprine dose was increased to 150 mg/d and her prednisone was stopped 4 months later. The total prednisone dose was 116,800 mg and azathioprine was used for 112 weeks (still in use).

**Case 4** – Had been receiving prednisone for 3 years; he also had courses of thalidomide. A year after stopping MDT he continued to have ENL and azathioprine (150 mg/d) was introduced, then it was possible to reduce prednisone to 20 mg/d, but the reduction in frequency and severity of episodes occurred only after 20 weeks. The total prednisone dose was 38,325 mg and he has been treated with azathioprine for 33 weeks (still in use).

**Case 5** – Presented with ENL at diagnosis and this continued for 5 years. The lowest dose of prednisone for controlling his ENL was 30 mg/d, with courses of thalidomide. In the last episode (02/09), 3 years after stopping, he was started on azathioprine 150 mg/d together with prednisone 60 mg/d. After 4 months the prednisone dose had reached 10 mg/d. The total prednisone dose was 73,000 mg and azathioprine has been used for 28 weeks (still in use).

**Case 6** – Had been taking thalidomide and prednisone with poor control of reactional episodes. He was released from MDT a year ago and he had no evidence of previous liver function impairment. He had an asymptomatic three fold increase of liver enzyme levels three weeks after starting azathioprine (100 mg/d). Serological tests for viral hepatitis were negative and the drug was withdrawn. The total prednisone dose was 38,300 mg and he took azathioprine for 3 weeks.

**Case 7** – Azathioprine (150 mg/d) was introduced 2 months after starting MDT (due to severe ENL) together with methylprednisolone pulsetherapy, followed by prednisone and thalidomide 300 mg/d (1999). After 9 months prednisone was reduced to 5 mg/d. He remained GCS-free for 2 years, until a new episode occurred, at which point prednisone and azathioprine were reintroduced at the same dose for 6 months. He was the only patient who had two separate courses of azathioprine with an interval. The total prednisone dose was 10,000 mg and he has been using azathioprine for 110 weeks (still in use).

**Case 8** – At diagnosis, due to a severe reaction, azathioprine (100 mg/d) together with methylprednisolone pulse therapy and MDT were introduced, followed by prednisone and thalidomide. In 6 months the dose of prednisone was reduced to 5 mg/d. At this dose he had fewer and less severe reactions. This patient had thrombocytopenia. The total prednisone dose was 6075 mg and azathioprine has been used for 110 weeks (still in use).
Case 9 – Had a severe ENL at diagnosis and was treated with azathioprine (100 mg/d) together with prednisone 60 mg/d and thalidomide 300 mg/d. After 6 months it was possible to reduce prednisone to 10 mg/d. The total prednisone dose was 4650 mg and azathioprine has been used for 33 weeks (still in use).

Discussion

There are few reports on the use of azathioprine in leprosy reactions. The only controlled study was carried out with Type 1 reactions, in which azathioprine was used in an 8 week course with prednisolone, and was as effective in the reaction management as prednisolone alone. In type 2 reactions, 3 case descriptions (five cases altogether) reported a better control of reactions when azathioprine was added to GCS therapy.

The drug was well tolerated, and the occurrence of hepatitis was an unfortunate coincidence in such a small number of patients, since it can be considered an uncommon side effect occurring in 0.30% of cases.

There is a large individual variability in the response to azathioprine, and the risk of toxicity is related to genetic polymorphisms in metabolic enzymes. Activity of two enzymes: thiorpurine s-methyltransferase (TPMT), a highly polymorphic enzyme, and xanthine oxidase (XO), produces inactive metabolites. Decreased TPMT or XO activity results in increased production of toxic metabolites. A TPMT value is recommended before introducing azathioprine to avoid potentially fatal myelotoxicity. TPMT enzyme activity may also be useful to determine the initial dose. This great variability might be responsible for reports of lack of drug efficiency. Unfortunately, we were unable to perform this test. In the evaluation of azathioprine effectiveness, its late onset of action must still be taken into account. This onset is known to take place around the eighth week, however in a meta-analysis on the use of azathioprine in Crohn’s disease, when analysing effectiveness and duration of therapy, the odds ratio reached statistical significance in the 17th week.

Unfortunately, it is noteworthy that a better control of leprosy reactions with azathioprine prevented the progression of neural damage, but there was no recovery of lost neural functions.

Our observation, although uncontrolled, and with few cases, indicates that azathioprine is a promising drug in the control of Type 2 reactions, and especially promising as a GCS sparing agent. Future controlled studies are needed to confirm this statement. Basic research in the immunology of leprosy reactions remains crucial for their understanding and for the development of more powerful drugs for their control and prevention.

References


