Azathioprine in the Treatment of Multiple Sclerosis: A Single Center Experience from Nepal

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ABSTRACT

Introduction: Azathioprine is used as an off - label drug for the treatment of multiple sclerosis. It is one of the oldest and most widely used immunosuppressants that targets T and B lymphocytes and thus reduces the relapse and slows down the disease progression with the almost same efficacy as the other disease modifying drugs for multiple sclerosis. But due to its side effect profile it isn't used as a standard choice of treatment. However, its cost effectiveness and oral route of administration makes it a drug of choice in a low socioeconomic country. This paper highlights the diagnosis of Multiple Sclerosis based on McDonald's criteria and treatment with Azathioprine.

Methods: It is a retrospective analysis was conducted among 32 patients suffering from Multiple sclerosis and treated with Azathioprine at tertiary neurological institue.Patients outcome was also documented reaching them individually.

Results: Among 19 patients all were female with highest prevalence among age group of 30-39 years old. 60% had relapsing remitting Multiple sclerosis, 45% of the patients present with ocular symptoms followed by 31% patients with lower limb weakness and spasticity. 30% did not develop any relapse, 15.8% patients developed one episode of relapse, 21.1% patients relapsed twice while 21.1% patients relapsed thrice during the study period. 85% patients showed signs of improvements with Azathioprine therapy in terms of decreased neurological residual deficits and less complication.

Conclusion: Azathioprine shows improvement, slows the rate of relapse with minimal evidence of side effects and no evidence of malignancy in patients with multiple sclerosis.

Key Words: Azathioprine; Interferon; Multiple Sclerosis.

INTRODUCTION

Multiple Sclerosis (MS) is an autoimmune inflammatory demyelinating disease of the central nervous system with axonal demyelination. It mostly affects young adults with average age of 20 - 30 years and more commonly affects females with female to male ratio of 3:1. The worldwide prevalence is around 5 -300 per 100000 people with an increase in higher latitudes. Diagnoses are made according to McDonald Criteria 2017 which includes signs and symptoms, radiological findings, and oligoclonal bands in the Cerebrospinal fluid. MS is classified into 4 types, clinically isolated syndrome, relapsing remitting, secondary progressive and primary progressive.[1]

The disease progression leads to physical disability, cognitive impairment and other symptoms that affect the quality of life.[2] Nepal is also a victim of this disease without known prevalence. Multi-disciplinary approaches in the treatment which includes disease modifying therapy, symptomatic treatment, lifestyle modification, rehabilitation, psychological support is being performed. The disease modifying drugs used at present are interferons, glatiramer acetate, teriflunomide, sphingosine1-phosphate receptor modulators, dimethyl fumarate, cladribine, and 3 types of monoclonal antibodies including ocrelizumab.

Among these drugs interferon is available in Nepal at high cost. Azathioprine was widely used as an effective treatment of MS in the early 1990s, but its use has been gradually decreased due to its adverse effect and

availability of other more potent and effective medications. Azathioprine is used as immunosuppressant in underprivileged patients because it is available and economical in comparison to Interferon and has been shown to be non-inferior to interferon in limited studies. In this study, we aim to describe the outcomes of MS patients treated with Azathioprine.

METHODS

This was a retrospective study done among 19 patients with multiple sclerosis being treated at Annapurna Neurological Institute and Allied Sciences (ANIAS) since 2013 AD. For the data collection electronic database was used. Baseline data including age, sex, presenting complaints, subtypes of MS, comorbid conditions, MRI, and CSF findings including positivity of oligoclonal bands, drug treatment received, number of relapses, and other laboratory findings. All the patients were reached out through phone calls to know about the present condition of the patient and their status since their last visit to the hospital.

Patients were diagnosed with MS based on McDonald's criteria. Patients who presented with clinical signs and symptoms of MS were diagnosed with the presence of demyelinating lesions in Magnetic Resonance Imaging not explained by any other causes followed by supportive evidence of positivity for oligoclonal bands in CSF. Patient diagnosed with clinical, laboratory or imaging criteria of MS and using AZT for maintenance treatment were included for the study subject whereas patient diagnosed with MS but received any treatment other than AZT as maintenance therapies were excluded from the study.

Patients were followed up at regular intervals during the study period to monitor the side effects of Azathioprine therapy as well as to monitor the progression of MS (remission, relapses, or progression). If the patient relapsed while on Azathioprine therapy, they were treated with steroids during the acute period and restarted on Azathioprine therapy at different higher doses. If any patient experienced side effects of Azathioprine therapy, the dose of Azathioprine therapy was reduced. The outcomes were to assess the number of relapses. Similarly, Secondary outcomes were the demographic profile, subtypes of MS, side effects of Azathioprine therapy, positivity for oligoclonal bands.

All these information was updated in the excel sheet and analyzed using SPSS. Descriptive statistics were expressed in terms of percentages. The study was approved by the Institutional Review Board of ANIAS.

RESULTS

A total of 32 patients were diagnosed with MS during the study period. However, only 13 of them could afford current standard treatment i.e., IFN or glatiramer acetate. Hence, 19 patients treated with Azathioprine were considered for this study. All 19 patients included in this study were female.12 patients (60%) had relapsing remitting MS, 3 (16%) had no relapse, 1 (5%) had clinically isolated syndrome and 1 (5%) had benign multiple sclerosis. The highest prevalence of MS was present in the age group 30-39 years with 7 (37%), followed by 6 (30%) in the age group 20-29 years and 5 (25%) in the 40-49 years group. Most of the patients presented with ocular symptoms (vision loss, blurring, diplopia) were present in 9 (45%) patients followed by lower limb weakness and spasticity in 6 cases. Facial numbness, facial paralysis, headache, loss of consciousness were other common presenting complaints. (Table 1)

Table 1 : Demographic and Clinical Characteristics of Participants

Variables	Frequency	Percentage
Age Group		
10-19	1	5%
20-29	6	32%
30-39	7	37%
40-49	5	27%
Symptoms		
Ocular	4	21%
Ocular+Sensory+ Cranial Nerve	1	5%
Ocular+ UMN Signs	2	10.5%
UMN Sign+Sensory	2	10.5%
Ocular+ UMN Signs+ Urinary	1	5%
Cerebellar	2	10.5%
Sensory Only	2	10.5%
Headache	1	5%
Pain	2	10.5
Ocular Symptom+ Seizure	1	5%
UMN Sign only	1	5%
Type		
Remitting & Relapsing	13	68%
Clinically Isolated	2	10%
Benign Multiple Sclerosis	1	5%
No Relapse	3	16%

Frequency		
1 episode	6	32%
2 episode	3	16%
3 episode	4	21%
4 episode	4	21%
5 episode	1	5%
9 episode	1	5%
Relapse Duration		
Within 1 year	12	63%
1-2 years	2	10.5%
2-3 years	1	5%
No Relapse	4	21%
Improvement		
Improved	16	84.2%
Not Improved	2	10.5%
Death	1	5.3%

When the clinical features were suspicious of MS, MRI was done (Figure 1) which showed cerebral involvement in 5 cases (26.4%), spinal cord involvement in 7 cases (36.9%), whereas 4 cases (21.1%) showed both spinal as well as cerebral involvement.

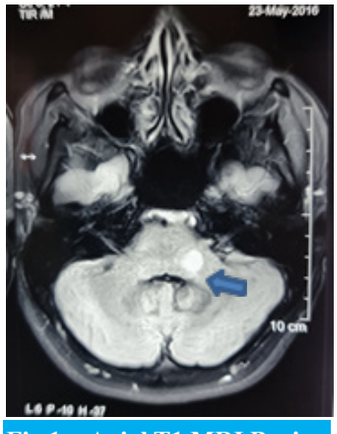

Fig 1a: Axial T1 MRI Brain

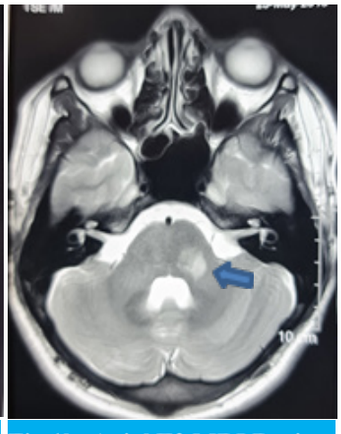

Fig 1b: Axial T2 MRI Brain

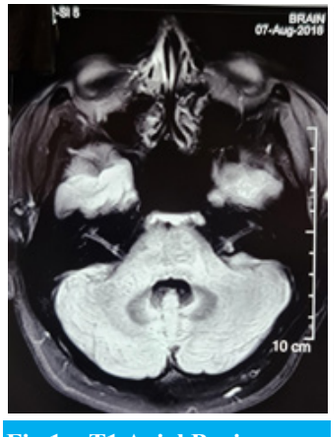

Fig 1c: T1 Axial Brain Post Azathioprine

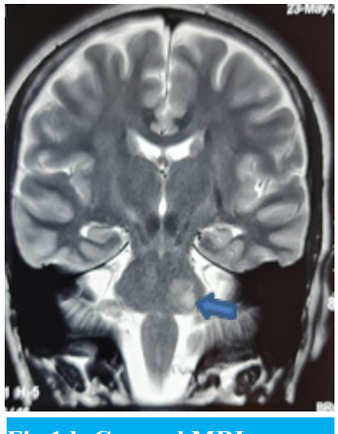

Fig 1d: Coronal MRI with lesion

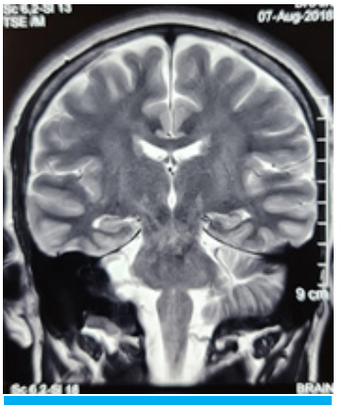

Fig 1e: Coronal MRI Post Azathioprine

2 cases (10.5%) did not show any MRI changes. Oligoclonal bands in CSF were detected in 12 cases. 6 patients (30%) did not develop any relapse, 3 patients (15.8%) developed one episode of relapse, 4 patients (21.1%) relapsed twice while 4 patients (21.1%) relapsed thrice during the study period. 1 patient (5.3%) each relapsed 4 and 8 times each. 17 patients (85%) showed signs of improvements with Azathioprine therapy in terms of decreased neurological residual deficits.

In terms of side effects, the patients were monitored during every follow up with the repeat blood tests, examination and history taking, no significant side effects and no evidence of post medication malignancy has been noticed in any patient.

DISCUSSION

MS is the most common immune-mediated inflammatory condition of the central nervous system characterized pathologically by multifocal areas of demyelination with loss of oligodendrocytes and astroglial scarring. The prevalence of MS in Nepal is not known. And many patients often get misdiagnosed due to limited awareness among the clinicians and paucity of neurologists in the country. Even when the correct diagnosis is made, clinicians are faced with challenges due to high costs associated with diagnosis and treatment including those of immunomodulatory agents like interferon or glatiramer acetate. In such a scenario, Azathioprine has proven life saving for patients with MS in resource poor countries like Nepal. In this study, we share the outcomes of using Azathioprine in patients diagnosed with MS at our center in the past 10 years. Limited data from our study shows that Azathioprine can be as effective alternative to modern immunomodulatory agents in preventing disability progression, relapses with manageable side effects.

Azathioprine is the most widely used immunosuppressive treatment in MS and is a cheaper alternative to interferon beta, the current standard treatment.[3,4] In a Cochrane network meta-analysis, interferon and Natalizumab were shown to be superior to all other agents from preventing clinical relapses in RRMS in the short term (24 months) compared to placebo. In the same study, Azathioprine

was shown to decrease the odds of patients with RRMS having relapses and disability progression over 24 to 36 months compared to placebo.[5] Azathioprine is a purine antagonist that affects DNA replication and impairs T-lymphocyte function and has been used in several chronic inflammatory and autoimmune diseases with good success. Azathioprine has been used for the treatment of MS for over three decades now.[6] Although newer immunomodulatory agents like interferon beta and glatiramer acetate have been introduced into clinical practice, their high costs and uncertain effects on long term disability progression means that azathioprine continue to thrive in clinical practice even today.[7] Very high costs render newer agents unaffordable for many in low- and middle-income countries (LMICs.).[8] Therefore, clinicians continue to use Azathioprine in clinical practice in LMICs.

A review of seven studies in 1991 found that Azathioprine was efficacious in preventing relapses at one, two and three years and had a slight borderline benefit on preventing disability progression at two and three years.[9] In a post marketing review by Palace et al, the probability to be free from relapses at two years in MS patients treated with interferon beta, glatiramer acetate, or intravenous immunoglobulins with that reported with Azathioprine in Yudkin's study concluded that these treatments were equivalent.[10]

In a recent Cochrane review including 698 patients diagnosed with variable forms of MS, Azathioprine was found to reduce the number of patients who had relapses during the first year of treatment (relative risk reduction [RRR] =20%; 95% CI = 5% to 33%), at two years' (RRR =23%; 95% CI = 12% to 33%) and three years' (RRR =18%; 95% CI = 7% to 27%) follow-up.[11] In a recent randomized controlled trial involving 127 RRMS patients, annualized relapse rate was 0.26 (95% Confidence Interval, CI, 0.19–0.37) in the azathioprine and 0.39 (95% CI 0.30–0.51) in the interferon group. Non-inferiority analysis showed that azathioprine was at least as effective as beta interferons (relapse RRAZA/IFN 0.67, one-sided 95% CI 0.96; p,0.01).[12] Further, in another study by Massacesi et al.[13] , Azathioprine was shown to reduce the new brain inflammatory lesion as evidenced by reduction in T2 weighted lesions (p <0.02)(13).

Further, due to the oral route of administration of Azathioprine, low cost to healthcare providers, Azathioprine may serve as an alternative form of treatment for patients with RRMS. However, there are few disadvantages associated with the long-term use of Azathioprine including gastrointestinal disturbances, bone marrow suppression, hepatic toxicity, and long-term risk of cancer.[14]

There are several limitations of our study. First, the sample size is very small to draw definite conclusions about the efficacy of Azathioprine. However, the cases diagnosed in our setting remains very less due to limited diagnostic capabilities and resources and affordability of patients. Hence, this truly highlights that Azathioprine can be a feasible option for treatment of MS patients. Second the severity of the disease condition has not been mentioned making the measurement of efficacy of Azathioprine less scientific and rigorous.

Head-to-head randomized controlled trial comparing Azathioprine to other standard treatment are essential to establish the establish efficacy of Azathioprine in MS. Further, it is essential that LMICs support the use of low cost biosimilars and encourage research based on their population and needs to enhance better care for MS patients.

CONCLUSION

Considering the socio-economic status, Azathioprine can be a useful option for patient suffering from MS. The higher price of standard treatment is potentially risk for patient to drop out from treatment. The side effects of Azathioprine can be monitored easily by routine blood investigations and patient need not visit primary center each time. Finally the the easy administration of this medicine makes it easier to persuade patients for adherence for the treatment.

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