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Clinical Study

Azathioprine plus corticosteroid treatment in Chinese patients with neuromyelitis optica

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ABSTRACT

We investigated the efficacy of azathioprine (AZA) plus long-term low dose corticosteroids in Chinese patients with neuromyelitis optica (NMO) and neuromyelitis optica spectrum disorders (NMOSD) at the Center for Demyelinating Diseases, South China. We prospectively enrolled patients between June 2010 and June 2014. Annualized relapse rate (ARR), expanded disability status scale (EDSS) score and modified Rankin Scale (mRS) were analyzed retrospectively. Of 77 patients with NMO/NMOSD (four males, 73 females; age range: 4–69 years), median disease duration before initiation of AZA was 32.0 months (range: 2.0–197.0). Median post-treatment follow-up was 23 months (range: 6–58) and 44 patients (57.1%) were relapse-free at median follow-up 19 months (range: 6–51). Pre-treatment ARR was 0.923, and post-treatment ARR was 0 ($p < 0.0001$). Survival analysis indicated a significantly lower risk of relapse (hazard ratio 0.522; 95% confidence interval 0.377–0.722; $p < 0.0001$). Significant improvements were shown in the EDSS (3.0 *versus* 1.0; $p < 0.0001$) and mRS (2.0 *versus* 1.0; $p < 0.0001$). Our study provides evidence supporting the use of AZA plus a low dose corticosteroid as an effective and safe strategy which is associated with a reduction in the risk of relapse in Chinese patients with NMO.

1. Introduction

Neuromyelitis optica (NMO) and neuromyelitis optica spectrum disorders (NMOSD) are characterized by the presence of anti-aquaporin 4 (AQP4) antibodies (NMO-IgG) in the serum and have a pathogenesis distinct from classical multiple sclerosis (MS) [1,2]. Unlike MS, most patients with NMO/NMOSD experience a relapsing course without marked remission. Risk of a progressive increase in disability makes NMO/NMOSD a devastating disease in social and economic terms.

NMO was once thought to be a rare disorder compared to MS. However, after NMO-IgG testing became available, increasing numbers of NMO/NMOSD patients are reported, specifically in Asian populations, probably due to genetic susceptibility and a large population base. Before introduction of the NMO-IgG test, in China and some Asian countries, NMO was often diagnosed as MS because of the limited awareness of NMO as well as partial overlap of the clinicoradiological features of the two disorders.

Clinical and experimental evidence supports the hypothesis that an abnormal immune response is a factor in the pathogenesis of NMO. Some studies have shown the efficacy of off-label prescription of immunosuppressants against NMO [3] including azathioprine (AZA) [4–6], mitoxantrone [7], methotrexate [8,9], corticosteroids [10] and mycophenolate mofetil [11]. However, a well-defined protocol for choosing the most appropriate treatment is lacking and the decision taken by the neurologist may depend on the availability and cost of a drug.

AZA, an imidazolyl derivative of mercaptopurine and an immunosuppressant, acts by reducing purine metabolism and inhibiting the synthesis of DNA, RNA and proteins. AZA given alone or as an adjunct to a corticosteroid has been shown to be effective against MS [12] and myasthenia gravis [13]. Since its use was first described seven patients with NMO who remained relapse-free over 18 months [4], three additional studies have been undertaken to validate the results [5,6,14]. Developing countries in Asia have

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limited medical resources and face challenges in treating NMO/NMOSD patients as increasing numbers are diagnosed and reported. Efficacy data for AZA in NMO/NMOSD are of critical importance, but data from Asian NMO/NMOSD populations are scarce. Therefore, we undertook a retrospective study to investigate the efficacy and safety of AZA plus low dose corticosteroids in a prospectively enrolled hospital-based NMO cohort from a tertiary referral center (Center for Demyelinating Diseases) in South China [15].

2. Patients and methods

2.1. Patients

Criteria for starting AZA and corticosteroid therapy were as follows: patients with NMO [1] or NMOSD [2], seropositivity for NMO-IgG detected by an anti-AQP4 antibody assay on an anti-AQP4 transfected cell line from a commercial Biochip kit (Euroimmun, Lübeck, Germany); normal genotype profiles for thiopurine methyltransferase (TPMT); not contraindicated for treatment using AZA or corticosteroid; effective female contraception. The study was approved by the Ethics Committee of the Third Affiliated Hospital of Sun Yat-sen University. Written informed consent was obtained from all study participants.

2.2. Treatment protocol

The treatment protocol was based on the experience of Mandler et al. with dose modification [4]. Briefly, AZA (Imuran; Heumann Pharma GmbH, Nürnberg, Germany) was started at 25 mg or 50 mg daily and increased to 2 mg/kg (50 mg or 100 mg) daily 2 weeks later. Corticosteroid treatment was started as methylprednisolone (Medrol; Pfizer, New York, NY, USA) at approximately 0.4 mg/kg/day. This dose was maintained for 8 weeks. Then, slow tapering was initiated with reductions of 4 mg every 3 weeks followed by a switch to alternate day treatment of 4–12 mg for long-term maintenance. In the acute relapsing stage, high dose intravenous methylprednisolone (IVMP) was administered at 500 mg or 1000 mg daily for five consecutive days followed by conversion to oral methylprednisolone daily. AZA plus methylprednisolone could be switched to AZA solely or methylprednisolone solely, or more aggressive therapy (for example, rituximab) depending on side effects and efficacy.

2.3. Efficacy assessment

Patients who had undergone $\geqslant$6 months of treatment were evaluated for drug efficacy. In each patient, neurological condition was assessed every 3 months by one of the authors (WQ) who also recorded the number of relapses. Unscheduled tests were also undertaken in patients with suspected relapse. Patient data before treatment were obtained from medical records.

The annualized relapse rate (ARR; calculated as the number of relapses divided by time in years), and disability (measured by the expanded disability status scale [EDSS] and modified Rankin scale [mRS]) before and after treatment were compared. Relapses were defined as objective worsening of neurological symptoms lasting $\geqslant$24 hours. Patients with suboptimal response to treatment were defined as those who had more relapses during the study than in the previous 2 years.

2.4. Adverse effects

Before administration of AZA we obtained TPMT genotype profiles (TPMT*2, TPMT*3A, TPMT*3B, TPMT*3C variants). AZA is contraindicated in patients with a mutation of the TPMT gene and other immunosuppressants (for example, methotrexate) are used. Baseline blood cell counts and liver function tests were checked before treatment and after the first 2 weeks and then monitored every 3 months during treatment. Adverse events or toxicity were managed by adjusting AZA doses if AZA-related side effects intervened. Criteria for stopping AZA treatment were liver dysfunction (alanine aminotransferase >20 U/L), leukopenia (white blood cell count $<2.5 \times 10^9$/L), anemia (hematocrit <30%), or serious infections.

2.5. Statistical analyses

Scores for the ARR, EDSS and mRS before and after treatment were compared using the Wilcoxon signed rank test. The Cox proportional hazard model for recurrent events was done using the counting process approach to compare curves pre and post-AZA after adjustment for age. Factors associated with a response were analyzed using the chi-squared or Mann–Whitney u-test. All statistical analyses were carried out using statistical software R (version 3.0.2; Vienna University of Economics and Business, Vienna, Austria) and $p < 0.05$ was considered statistically significant.

3. Results

3.1. Demographic data

One hundred and four consecutive patients were started on AZA plus corticosteroid treatment and followed up. Of these, 77 patients (four males and 73 females; age range: 4–69 years) with two or more disease attacks in the previous 2 years were enrolled for the analysis (Table 1). Those patients excluded from the analysis were 16 patients with prior exposure to other immunosuppressants in the preceding year, four patients with a first attack (two optic neuritis, two longitudinal extensive myelitis), four patients who switched from AZA plus corticosteroids to AZA alone because of the adverse effects of corticosteroids presented below, two patients who discontinued AZA and switched to rituximab, and one patient who died from respiratory failure after treatment for 2 months.

3.2. Efficacy of treatment

Of the 77 patients who were administered AZA plus corticosteroids, 63 (81.8%) were treated for >1 year and 37 (48.1%) for >2 years. Forty-four (57.1%) patients were relapse-free after a mean follow-up of 20 months (range: 6–51; Fig. 1; Table 2). Mean pre-treatment ARR was 0.923 (range: 0.1–6.0), and

Table 1
Demographic data of 77 NMO/NMOSD patients undertaking a regimen of azathioprine plus corticosteroid (median (range))

Protocol	AZA + CS
Phenotype (NMO/NMOSD)	58/19
Sex, female:male	73:4
Age at first symptoms, years	32 (4–69)
Age at final follow-up, years	39 (5–71)
Duration before AZA, months	32 (2–197)
Duration of AZA use, months	23 (6–58)
ARR before AZA	0.92 (0.1–6.0)
EDSS before AZA	3.0 (1.0–9.0)
mRS before AZA	2.0 (1.0–5.0)

Values are presented as the median (range), unless otherwise stated.
ARR = annualized relapse rate, AZA = azathioprine, CS = low dose corticosteroid, EDSS = expanded disability status scale, mRS = modified Rankin scale, NMO/NMOSD = neuromyelitis optica/neuromyelitis optica spectrum disorder.