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ARTICLE

Long-term safety of azathioprine for treatment of neuromyelitis optica spectrum disorders

Segurança a longo prazo da azatioprina no tratamento dos transtornos do espectro da neuromielite óptica

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ABSTRACT

Background: Azathioprine is a common first-line therapy for neuromyelitis optica spectrum disorder (NMOSD). **Objective:** The aim of this study was to determine whether long-term treatment (>10 years) with azathioprine is safe in NMOSD. **Methods:** We conducted a retrospective medical record review of all patients at the School of Medicine of the University of São Paulo (São Paulo, Brazil) who fulfilled the 2015 international consensus diagnostic criteria for NMOSD and were treated with azathioprine for at least 10 years. **Results:** Out of 375 patients assessed for eligibility, 19 were included in this analysis. These patients' median age was 44 years (range=28–61); they were mostly female (17/19) and AQP4-IgG seropositive (18/19). The median disease duration was 15 years (range=10–39) and most patients presented a relapsing clinical course (84.2%). The median duration of treatment was 11.9 years (range=10.0–23.8). The median annualized relapse rates (ARR) pre- and post-treatment with azathioprine were 1 (range=0.1–2) and 0.1 (range=0–0.35); p=0.09. Three patients (15.7%) had records of adverse events during the follow-up, which consisted of chronic B12 vitamin deficiency, pulmonary tuberculosis and breast cancer. **Conclusion:** Azathioprine may be considered a safe agent for long-term treatment (>10 years) of NMOSD, but continuous vigilance for infections and malignancies is required.

Keywords: Azathioprine; Neuromyelitis Optica; Therapeutics.

RESUMO

Introdução: A azatioprina é um tratamento comum de primeira linha para os transtornos do espectro neuromielite óptica (NMOSD). **Objetivo:** Este estudo visou determinar a segurança do tratamento a longo prazo (>10 anos) da NMOSD com a azatioprina. **Métodos:** Foi realizada revisão retrospectiva de todos os prontuários de pacientes que preenchiam critérios de NMOSD de acordo com o "International Consensus Diagnostic Criteria for NMOSD" de 2015 em uso de azatioprina por ao menos 10 anos matriculados no ambulatório de Doenças Desmielinizantes do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo. **Resultados:** De 375 pacientes avaliados, 19 preencheram critérios de inclusão para análise. A mediana de idade foi de 44 anos (variância=28–61); os pacientes eram predominantemente do sexo feminino (17/19) e AQP4-IgG soropositivos (18/19). A mediana do tempo de duração de doença foi 11,9 anos (variância=10,0–23,8), a mediana da taxa anualizada de surtos pré e pós-tratamento foi de 1 (variância=0,1–2) e 0,1 (variância=0–0,35), p=0,09. Três pacientes (15,7%) apresentaram registro de eventos adversos durante o seguimento: deficiência crônica de vitamina B12, tuberculose pulmonar e câncer de mama. **Conclusão:** A azatioprina provavelmente pode ser considerada segura para o tratamento a longo prazo (>10 anos) da NMOSD, porém vigilância contínua de neoplasias e infecções é necessária.

Palavras-chave: Azatioprina; Neuromielite Óptica; Terapêutica.

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INTRODUCTION

Neuromyelitis optica spectrum disorders (NMOSD) are severe inflammatory diseases of the central nervous system that are estimated to affect 0.52 to 4.4 individuals per 100,000 worldwide[1]. Its prevalence and disease phenotypes are influenced by ethnicity, with worse clinical outcomes associated with Asians, Africans and Latin Americans[2]. Preventive therapy is achieved through immunosuppression with agents such as azathioprine, mycophenolate, methotrexate and corticosteroids, or B-cell modulation with rituximab[3].

NMOSD is a rare disorder with scarce evidence in the literature to guide treatment decision-making. Most studies come from developed countries, where rituximab and mycophenolate are commonly used as first-line therapies. In resource-limited settings, such as low- and middle-income countries, azathioprine is often used as first-line care, with reductions in annualized relapse rate (ARR) ranging from 70 to 74% and an approximate 80% chance of reduction in the hazard of disability progression after five years[4,5,6,7].

In studies on multiple sclerosis (MS), an increased risk of development of malignancies in patients with over 10 years of continuous therapy or cumulative doses of azathioprine superior to 600 g has been reported[8,9]. The long-term safety of azathioprine has never been assessed in the NMOSD population.

In this study, we report on the long-term safety of treatment with azathioprine for NMOSD in our reference center in São Paulo, Brazil.

METHODS

We retrospectively reviewed the medical records of all consecutively assessed patients followed at the NMOSD outpatient clinic at the School of Medicine of the Universidade of São Paulo (São Paulo, Brazil), from January 2005 to May 2017, who fulfilled the 2015 international consensus diagnostic criteria for NMOSD[10]. Patients treated with azathioprine for 10 consecutive years or more were included in this analysis. All of these patients had received 2-3 mg/kg/day of azathioprine during this period. Azathioprine had been slowly introduced in order to mitigate hematological and hepatic side effects.

All records were assessed for 1) demographics; 2) baseline clinical information; 3) treatment details (date of start and end of therapy and adverse events); and 4) clinical course (dates of relapses and ARR). The review was performed by a neurologist experienced in the application of the 2015 international consensus diagnostic criteria for NMOSD[10]. Patients with incomplete records were not included in the analysis.

A descriptive statistical analysis was performed. The Wilcoxon-Mann-Whitney test was used for comparing pre- and post-treatment annualized relapse rates (ARR). P-values<0.05 were considered significant.

This study received approval from the local university research ethics committee (reference no. 2.904.151). Participants were not required to provide informed consent, given that this was a retrospective study.

RESULTS

Out of 375 records reviewed, 19 patients met the inclusion criteria (5%). These patients were mostly female (17/19) and AQP4-IgG seropositive (18/19). One patient with AQP4-IgG seronegative NMOSD was also included in the analysis. Briefly, this patient had a history of seven typical attacks, including bilateral optic neuritis, longitudinally extensive transverse myelitis, acute brainstem syndrome and area postrema syndrome, which fulfilled the 2015 international consensus diagnostic criteria for NMOSD. AQP4-IgG was assessed after 20 continuous years of azathioprine treatment.

The median disease duration was 15 years (range=10–39); most patients presented a relapsing clinical course (84.2%). The median duration of treatment was 11.9 years (range=10.1–23.8) (Table 1). The median ARR pre- and post-treatment with azathioprine were 1 (range=0.1–2) and 0.1 (range=0–0.35); p=0.09 (Table 1 and Figure 1). Twelve patients (63.2%) had been free of relapses for at least 5 years.

Three patients (15.8%) had records of adverse events during the follow-up, which consisted of chronic B12 vitamin deficiency, pulmonary tuberculosis and breast cancer.

Table 1. Clinical, demographic and laboratory data for 19 patients with long-term treatment with azathioprine (>10 years).

Characteristic	
Sex (F:M)	17:2
Ethnicity, no. (%)	
Caucasian	6/19 (31.6%)
Afro descendant (Afro+Mulatto)	11/19 (57.9%)
Asian descendant	0/19 (0%)
American Indian descendant	2/19 (10.5%)
Age, median (range), y	44 (28–61)
AQP4-IgG serum status, no. (%)	
Positive	18/19 (94.7%)
Negative	1/19 (5.2%)
Clinical course, No. (%)	
Monophasic NMOSD	3 (15.8%)
Relapsing NMOSD	16 (84.2%)
Disease duration, median (range), y	15 (10–39)
Duration of treatment, median (range), y	11.9 (10.0–23.8)
Annualized relapse rate, median (range)	
Before azathioprine therapy	1 (0.1–2)
After azathioprine therapy	0.12 (0–0.35)

NMOSD, neuromyelitis optica spectrum disorders.

At the time of the review, 13 of the 19 patients (68.4%) were still receiving azathioprine. One patient had been switched to methotrexate due to long exposure to azathioprine; one patient to rituximab due to therapy failure; and two patients to mycophenolate and cyclophosphamide due to rheumatological comorbidities (systemic sclerosis and systemic lupus erythematosus). Two patients had chosen to discontinue immunosuppression after approximately twelve years due to stability of the disease: both of these patients presented AQP4-IgG seropositive NMOSD with a single attack.

DISCUSSION

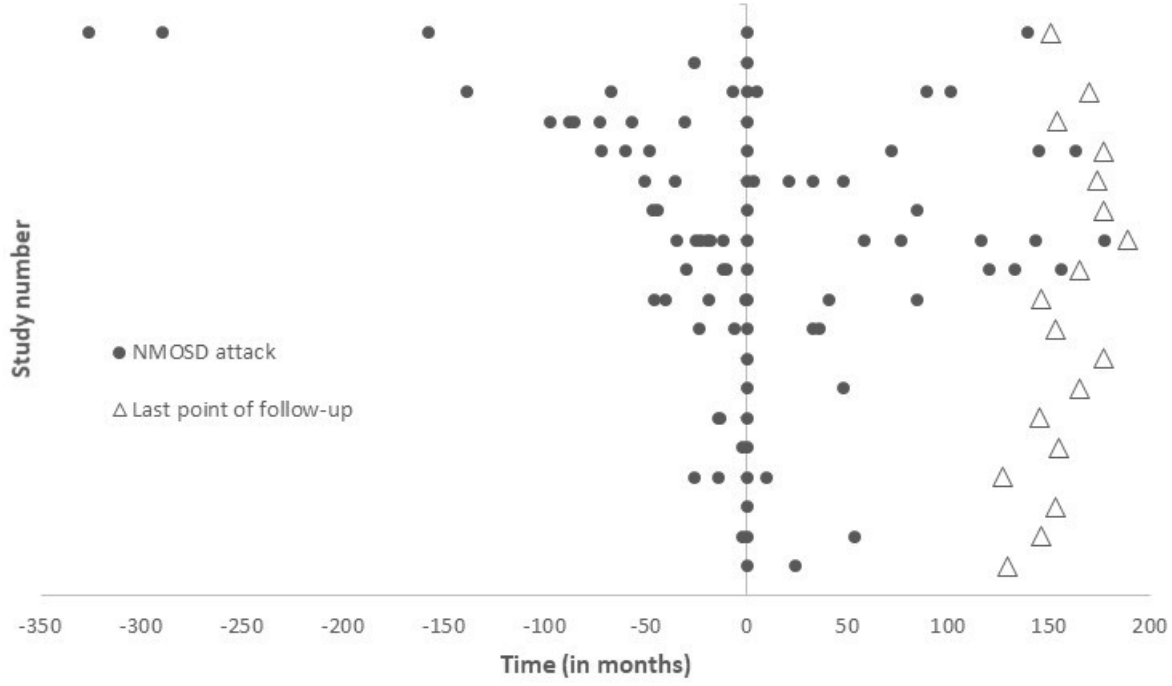
This is the first long follow-up safety report on NMOSD patients under azathioprine therapy. We decided to include patients with at least 10 consecutive years of therapy because that was the time range previously reported to lead to increased risk of malignancies in the MS population[8]. We had a small sample size (5%) due to our stringent inclusion criteria.

In our sample, there were three reports of adverse events, including one of malignancy (5.2%). The case of malignancy consisted of an invasive ductal carcinoma (breast cancer) in a 41-year-old female who responded well to a combination of surgery, radiation therapy and chemotherapy. The absolute risk of breast cancer development at that age is approximately 1.53%[10].

We also described the clinical course of our 19 patients while on azathioprine. Previous studies have indicated that a reduction in ARR occurs under azathioprine treatment[4,5,6]. Our study also suggests that this reduction in ARR occurs, but the sample was too small to draw conclusions regarding efficacy.

Although there are no previous studies discussing the long-term safety of azathioprine in the NMOSD population, data in the literature suggest that in the MS population this medication may present a dose-dependent relationship with an increased risk of developing malignancies[8]. In a case-control study involving 1,191 MS patients, Confavreux et al.[9] reported that there was a statistically non-significant increase in cancer risk of 1.3 (95% confidence interval [95%CI] 0.4–4.0) for MS patients when treated for less than 5 years; of 2.0 (95%CI 0.4–9.1) when treated for 5–10 years; and of 4.4 (95%CI 0.9–20.9) when treated for more than 10 years. In contrast, Amato et al.[11] did not find any increase in cancer risk in a cohort of 454 MS patients with age-adjusted occurrence rates of cancer of 3.62 per 1000 person-years in azathioprine-treated patients versus 4.24 per 1000 person-years in untreated patients, with a RR of 0.85. We found a single case of malignancy among these 19 patients under azathioprine treatment for periods of over 10 years.

Our study has several limitations. It was a small retrospective case series that required fulfillment of the 2015 diagnostic criteria for NMOSD[12] and included only patients treated with azathioprine at a dose of 2–3 mg/kg/day for at least 10 consecutive years. Patients who had early discontinuation of azathioprine due to treatment failure or adverse events such as hepatotoxicity or hematological dysfunction were not included in this analysis, although those findings have been reported in other series[5]. In addition, we did not perform any control-matched statistical analysis, which compromises the generalizability of our findings. Nonetheless, as NMOSD is a very rare disease that was recently described and there are currently no available publications assessing the long-term



NMOSD, neuromyelitis optica spectrum disorders.

Figure 1. Neuromyelitis optica spectrum disorder attacks among 19 patients pre- and post-azathioprine treatment (>10 years).

safety of azathioprine in this population, we believe our data to be valuable, especially in relation to healthcare systems where new therapies may not be fully or rapidly available.

Although it is widely accepted that patients with NMOSD should undergo preventive treatment, the length of treatment and drug regimen choice remain uncertain. Knowledge of the safety of long-term exposure to azathioprine may guide clinical management in resource-limited settings where access to other more expensive drugs such as monoclonal antibodies is restricted. In our service, all relapsing NMOSD patients with more than 10 continuous years of azathioprine therapy are kept on the drug but undergo yearly cancer screening. In our experience, this has proven to be a safe and effective treatment strategy.

In conclusion, our findings suggest that azathioprine may be considered a safe agent for long-term treatment (>10 years) of NMOSD. However, continuous vigilance for infections and malignancies is required. Due to its low-cost and easy access, azathioprine may be a reasonable treatment option in resource-limited settings. Further prospective controlled studies looking into the long-term safety of immunosuppressants in NMOSD are warranted, to confirm these findings.

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