Section: Neurology

Original Research Article

RITUXIMAB VERSUS AZATHIOPRINE IN PROPHYLAXIS OF SEROPOSITIVE NEUROMYELITIS OPTICA SPECTRUM DISEASE (NMOSD): A PROSPECTIVE STUDY FROM EASTERN INDIA

S. Mishra[1], A Satapathy[1], A.K. Mallick[2]

[1]Assistant Professor, Department of Neurology, Hitech Medical College, Bhubaneswar, India
[2]Professor, Department of Neurology, S.C.B Medical College, Cuttack India

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Corresponding Author:
Dr. S. Mishra,
Email: dr.subham.scb@gmail.com

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Abstract

Background: Neuromyelitis Optica Spectrum disorder (NMOSD) is an autoimmune chronic inflammatory disorder of CNS. Rituximab and azathioprine are two primary drugs for maintenance therapy. The objective of this study was to isolate cases of aquaporin-positive NMOSD, treat them according to recent guidelines, and follow up to compare the efficacy of rituximab and azathioprine. **Materials and Methods:** Prospective randomised clinical study in S.C.B Medical College, Cuttack's neurology department from 2018-20. Seropositive NMOSD patients were diagnosed, and treated by acute and prophylactic therapy by Rituximab (RTX) and azathioprine (AZT) randomly. They were followed up for at least three years and an Expanded Disability Status Scale (EDSS) calculation was done. Statistical analysis was done using SPSS (Statistical Package for the Social Sciences) Software version 20. P value was considered significant if less than. **Result:** The total number of patients included in the study was 20. 8 patients were treated with prophylactic azathioprine therapy, whereas 12 patients were treated with rituximab therapy. At a minimum follow-up of 36 months, the median annualised post-treatment relapse rate was lower in the RTX group in comparison to AZT (0.04 vs 0.4 [range, 0-2] relapses, P < .001). Disability improved or stabilized significantly in RTX cohort. **Conclusion:** In NMO, treatment with rituximab appears to reduce the frequency of attacks, with subsequent stabilization or improvement in disability in comparison to azathioprine.

INTRODUCTION

Neuromyelitis optica spectrum disorder (NMOSD) is an acute neuroinflammatory disease of the central nervous system (CNS), predominantly affecting the optic nerve and the spinal cord.[1] Serum immunoglobulin G (IgG) autoantibody specific for the astrocyte water channel aquaporin- 4 (AQP4-IgG) is a biomarker for NMOSD.[2] NMOSD follows a relapsing course in more than 85–90% of cases, and frequent attacks may lead to severe disability with poor recovery.[1] Acute attacks are managed by administrating high doses of intravenous corticosteroids, intravenous immunoglobulins, and plasma exchange (PLEX).[1,3] For maintenance therapy, immunosuppressive agents are recommended including azathioprine (AZT), rituximab (RTX), mycophenolate mofetil, methotrexate, cyclophosphamide, mitoxantrone, and cyclosporine.[1,3] AZT is an antimetabolite affecting lymphocyte proliferation and is available in the oral form. Because of side effects such as bone marrow suppression and hepatotoxicity, periodic checks of blood cells and liver enzymes are needed.[4] RTX is a chimeric monoclonal antibody directed against CD20, a marker expressed by B cells, which decreases B lymphocytes and subsequently AQP4-IgG in patients.[5] Comparative studies between recommended drugs are all retrospective, and very rare clinical trials have to our knowledge, been conducted. Therefore, we aimed to compare the efficacy of administrating AZA and RIT as maintenance therapy in NMOSD patients in a randomized clinical trial.

MATERIALS AND METHODS

This open-label randomised clinical study was conducted between 2018 and 2020 in the Department of Neurology of the S.C.B Medical College and Hospital, Odisha, India. The inclusion criteria were defined as a diagnosis of Seropositive NMOSD based on the international consensus diagnostic criteria in 2015.[3] Treatment by maintenance therapy by either

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AZT or RTX. Minimum follow-up duration of 3 years. The exclusion criteria were defined as patients who were dead or lost to follow-up. The patients who discontinued the medications. Patients who had other connective tissue disorders. The patients who didn't give consent for the study.

Patients who were included after seropositivity of Aquaporin 4 IgG (AQP4-IgG was determined previously for each patient qualitatively using a commercially available indirect immunofluorescence kit) were randomly divided into two groups of AZA and RTX by simple randomisation using a lottery. The study was not blinded. A complete history of the disease and a thorough physical examination were performed by an expert neurologist. AZA was started on the day of discharge at an adequate dose. It was continued with monitoring of blood parameters and liver function tests. Rituximab was injected after acute treatment with injectable methylprednisolone according to protocol. Rituximab injection was used every six months irrespective of CD19 Cell counts. We recorded patients' characteristics, including age and sex, before intervention. Numbers of previous relapses were also recorded. Expanded disability status scale (EDSS) was used before hospitalisation, at 3-month follow-up, 6-month follow-up, and 1-year follow-up. The two cohorts were compared using SPSS Software version 20.0. Expert advice was taken from a departmental statistician. Ethical clearance was obtained from the institutional ethical committee. [Methodology flow chart- Figure 1].

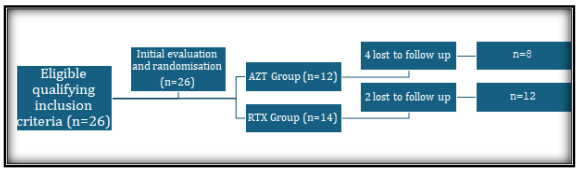

Figure 1: flow chart of case selection.

RESULTS

The total numbers of patients included in the AZA and RTX were 8 and 12. The mean age in the AZA group was 37.25 and 33.16 in the RTX Group. The male-to-female ratio was 1:1.6 in the AZA group, whereas it was 1:5 in the RTX Group. The average pre-treatment EDSS in the AZA group was 7.1, whereas in the RTX group 7.8. Post-treatment EDSS (3 m, 6 m, 1 yr) was compared. A significant decrease in EDSS was seen in the RTX group. ARR before treatment was 1 in the AZA Group. In the RTX group, it was 1.4. After prophylactic therapy, the ARR in AZA was 0.37, and in RTX, it was 0.04. ARR decrease was significant in the RTX group statistically. All results are summarised in the [Table 1 and Figure 2].

Table 1: cohort characteristics.

Characteristics	Cohort- 1 (AZA Group)	Cohort- 2 (RTX Group)	P- Value
Total patients	8	12	0.319
Mean age	37.25	33.16	
Male:Female	1:1.6	1:5	
Annual relapse rate - ARR (Pre-treatment)	1	1.4	
AVG.EDSS	7.1	7.8	
AVG EDSS (3m)	6	6.4	
AVG.EDSS (6m)	5.7	4.9	
AVG. EDSS (1yr)	5	4.3	
ARR	0.37	0.04	

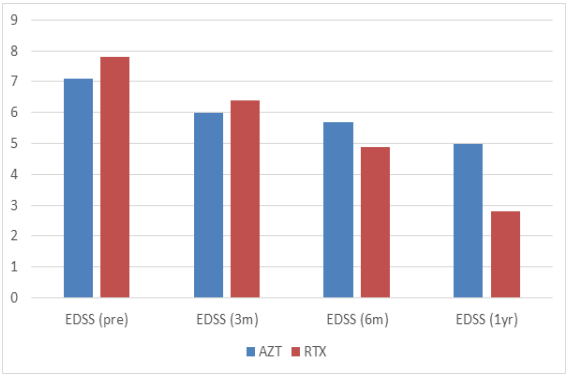

Figure 2: AVG. EDSS comparision

DISCUSSION

In this randomised study, we found significantly decreased ARR and EDSS among NMOSD patients in response to both AZA and RTX, although a more favourable response was observed in patients receiving RIT. AZA was first administered by Mandler et al. in seven newly diagnosed NMO patients in combination with oral prednisolone after a pulse of methylprednisolone.[7] They reported decreased mean EDSS from 8 at the baseline to 4 after 18 months of intervention, and no relapses happened during the study. Another prospective study in China evaluated the efficacy of azathioprine on 77 NMOSD patients and reported a decreased median of ARR (0.923–0) and EDSS (3–1) at the median follow-up after 19 months.[8] Cree et al. reported the first experience of RTX in NMOSD patients. They found a decreased median of ARR from 2.6 to 0 and a decreased median of EDSS from 7.5 to 5.5 (both P values <0.05) with relapse-freedom in six patients during an average 1 year of follow-up.[9] Jeong et al. studied 138 NMOSD patients retrospectively to compare the efficacy of AZA (49 cases), mycophenolate mofetil (34 cases), and RTX (55 cases) among them.[10] They reported a significantly higher risk of relapse in the azathioprine

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group compared to RTX group. This study also coincides in this fact.

CONCLUSION

AZA and RTX can both effectively decrease ARR and EDSS in seropositive NMOSD patients. However, rituximab was a superior treatment option, leading to drug discontinuation. Further studies with larger sample sizes and longer duration of follow-ups are required.

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