Neurology Asia 2026; 31(2) : 673 – 686

Clinical and immunomodulatory profiles of satralizumab and rituximab in AQP4-IgG+ NMOSD: A retrospective cohort study

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Abstract

Background & Objective: Seropositive neuromyelitis optica spectrum disorder (NMOSD) is characterized by frequent relapses and substantial disability rates. The efficacy and safety of existing drugs vary. There are relatively few direct comparative studies of satralizumab and rituximab. The objective of this study is to systematically compare the efficacy and immunomodulatory effects of satralizumab and rituximab in patients with NMOSD. *Methods:* A retrospective controlled study design was adopted to select 132 NMOSD patients hospitalized at The Second Hospital of Lanzhou University spanning January 2019 to December 2023. After exclusion, 129 cases were included, 3 cases were lost to follow-up, and 4 cases were excluded due to incomplete data. Finally, a total of 122 cases were analyzed and divided into Group A (rituximab treatment, 60 cases) and Group B (satralizumab treatment, 62 cases) according to the treatment plan. The primary observation indicators included Annualized Relapse Rate (ARR), recurrence time, changes in Expanded Disability Status Scale (EDSS) score, changes in AQP4-IgG concentration, Treg and CD20+ cell counts, and the secondary observation indicators included levels of inflammatory factors (IL-6, TNF-α), levels of IgG subclasses (IgG1, IgG3), incidence of adverse events, and quality of life score (SF-36). *Results:* Baseline data between the two patient groups were numerically indistinguishable, with the groups being comparable (P>0.05). After treatment, Group B had higher AQP4-IgG concentration, Treg cell count, CD20+ cell count, IgG1, IgG3, and SF-36-GH score than Group A (*95%CI*: -0.19--0.005, P=0.038; *95%CI*: -8.77--1.17, P=0.011; *95%CI*: -242.42--237.89, P<0.001; *95%CI*: -5.00--0.94, P=0.004; *95%CI*: -3.80--0.02, P=0.048; *95%CI*: -7.98--0.04, P=0.048); and Group B had numerically lower ARR, EDSS score, IL-6, and TNF-α than Group A (*95%CI*: 0.003-0.09, P=0.035; *95%CI*: 0.004-0.7, P=0.047; *95%CI*: 0.39-1.66, P=0.002; *95%CI*: 0.13-6.91, P=0.042). Group B had fewer adverse events were observed in the incidence of infusion/injection reactions and infection (*95%CI*: 1.10-25.63, P=0.023; *95%CI*: 0.94-22.71, P=0.042). The recurrence time in Group B was longer than that in Group A [*HR*: 1.77 (1.16, 2.72), P=0.006]

Conclusion: In this single-center retrospective cohort of AQP4-IgG+ NMOSD, satralizumab use was associated with lower ARR and EDSS at 18 months than those treated with rituximab, whereas rituximab was associated with greater peripheral CD20+ B-cell depletion. These are unadjusted observational associations and should be interpreted cautiously; prospective randomized studies are needed to confirm comparative effectiveness and safety.

Keywords: Satralizumab; rituximab; seropositive neuromyelitis optica spectrum disorder; immunomodulation

INTRODUCTION

Seropositive Neuromyelitis Optica Spectrum Disorder (NMOSD) is an autoimmune disease of the central nervous system where humoral immunity serves as the primary mediator, and it has thus emerged as a key area of interest in global neuroimmunology due to its high relapse rate and high disability rate.[1] The disease is mainly

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Date of Submission: 27 August 2025; Date of Acceptance: 5 January 2026

https://doi.org/10.54029/2026rsc

characterized by involvement of the optic nerve and spinal cord. Patients often present with acute vision loss, limb paralysis, sensory disturbance, and urinary and fecal dysfunction. Each relapse may lead to irreversible nerve injury, which seriously affects the quality of patients' lives.[2-4] According to epidemiological data, the annual relapse rate of seropositive NMOSD patients can be as high as 30%-40%, and after multiple relapses, approximately 60% of patients will experience permanent vision loss or difficulty in walking within 5 years, imposing a heavy burden on families and society. Therefore, exploring safe and effective treatment options to reduce the risk of relapse and delay disease progression has become the core issue of current clinical research.[2-5]

In the mechanism underlying the pathogenesis of seropositive NMOSD, the production of autoantibodies and activation of the complement system play key roles. Among them, aquaporin-4 antibody (AQP4-IgG) is a specific biomarker indicative of seropositive NMOSD. After binding to AQP4 within the structural framework of the central nervous system, it can trigger a series of immune response, including complement system activation, inflammatory cell infiltration, and blood-brain barrier disruption, ultimately leading to inflammatory injury of the optic nerve as well as the spinal cord.[6-8] Based on this mechanism, therapeutic strategies targeting immunomodulation have become an important direction for the prevention and treatment of seropositive NMOSD, and monoclonal antibodies have gradually become a hotspot in clinical research due to their advantages such as strong specificity and clear mechanism of action. Satralizumab, as a humanized monoclonal antibody, mainly exerts its effect by targeting and binding to the interleukin-6 receptor (IL-6R).[9] By blocking the bonding of IL-6 to IL-6R, satralizumab can effectively inhibit the IL-6-mediated immuno-inflammatory cascade, thereby curbing the production of AQP4-IgG and the inflammatory-mediated injury of the central nervous system. Multiple clinical studies have confirmed that satralizumab has significant efficacy in reducing the relapse rate and delaying disability progression in patients with seropositive NMOSD, with good safety.[10,11] Rituximab is a monoclonal antibody against the CD20 antigen that exerts immunomodulatory effects primarily through selective depletion of B lymphocytes. As a classic immunosuppressive agents, rituximab has long been employed in the management of seropositive NMOSD, and a large amount of clinical data show that it works to effectively decrease the risk of recurrence in patients and ameliorate their clinical signs.[12,13]

Although both satralizumab and rituximab have shown certain effectiveness in treating seropositive NMOSD, their mechanisms of action are different, and their efficacy and safety may vary. For example, satralizumab mainly targets the IL-6 pathway, while rituximab mainly targets B-cells, which may lead to differences in their efficacy response in different patient populations.[14] In addition, their administration methods, treatment courses, and long-term effects on immunisation function may also be different, and these factors can affect the choice of clinical treatment options. Currently, there are relatively few direct comparison studies on satralizumab and rituximab in seropositive NMOSD, and clinicians often lack sufficient evidence when choosing treatment options. Therefore, a systematic comparison of the efficacy of the two, including the relapse rate, the degree of disability progression, and the improvement of clinical symptoms, as well as analyzing their impact on immunomodulation, is of significant clinical importance. This will not only help provide more precise guidance for clinical treatment, optimize treatment regimens, and improve the treatment outcomes and patients' life quality, but also further deepen the comprehension of the pathogenesis of seropositive NMOSD, and offer a theoretical groundwork for the development of new therapeutic drugs and strategies.[15]

METHODS

General information

This study retrospectively selected 132 cases of seropositive NMOSD patients received into The Second Hospital of Lanzhou University during the period January 2019 to December 2023 as the research subjects, aiming to compare and evaluate the therapeutic effects of satralizumab and rituximab. As shown in the experimental flow chart in Fig. 1, after exclusion, 129 cases were included, 3 cases were lost to follow-up, and 4 cases were excluded due to incomplete data. Finally, a total of 122 cases were analyzed, and they were divided into Group A (rituximab treatment, 60 cases) and Group B (satralizumab treatment, 62 cases) according to different treatment regimens.

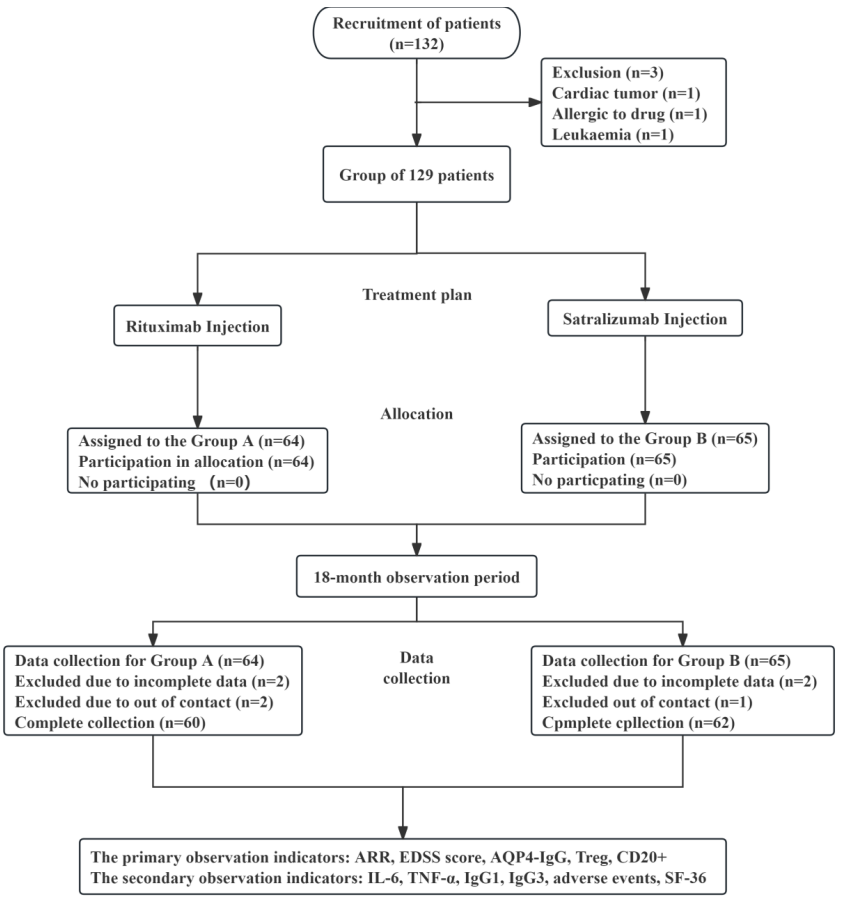

Figure 1. Experimental process design diagram

(The flowchart outlines the recruitment, inclusion, exclusion and allocation of patients. Eventually, 60 patients from Group A and 62 from Group B were enrolled to undergo analysis and comparison)

Inclusion criteria

(1) Patients must satisfy the diagnostic criteria for NMOSD in the "Chinese Guidelines for Diagnosis and Treatment of Neuromyelitis Optica Spectrum Disorder (2025 Edition)"[16] compiled by Chinese Journal of Neurology, Neuroimmunology Group of Chinese Society of Neurology, Chinese Medical Association; (2) AQP4-IgG test positive; (3) 18-75 years old; (4) Have at least one core clinical symptom, such as eye pain, visual function impairment, etc.; (5) Other diagnoses are excluded; (6) Have had at least one definite NMOSD attack in the past 1-2 years (doctors determine, based on clinical information and examination results, that the duration of newly occurring or worsening neurological deficits is ≥24 hours, with an interval of ≥30 days from the previous attack. Combined with magnetic resonance imaging examination, the presence of new lesions or enhancement of existing lesions is clearly confirmed.); (7) Patients have clinical needs for immunomodulatory therapy; (8) Patients have not started treatment with satralizumab or rituximab, or have discontinued other immunosuppressive agents that may affect the efficacy of the study drug for a sufficient period of time (usually more than 5 half-lives of the drug) to avoid interference with the study results from other drugs; (9) Complete clinical data and related investigation.[17,18]

Exclusion criteria

(1) Patients with other severe diseases or comorbidities; (2) Combined with other diseases of the nervous system; (3) A definite history of allergy to satralizumab, rituximab, or any of its excipients; (4) Female patients who are pregnant

or breastfeeding; (5) Abnormal immune function; (6) Mental illness or cognitive disorder; (7) Recent immunisation with live vaccine[18]; (8) Patients with contraindications to satralizumab or rituximab..

Treatment regimen

This study employed a retrospective controlled design, dividing patients into two groups based on treatment modality. Group A received rituximab treatment, encompassing 60 patients, while Group B received satralizumab treatment, encompassing 62 patients.

The specific administration methods are as follows:

The administration method for Group A was primarily intravenous infusion. rituximab Injection (Rituxan, SFDA approval number J20080054, F. Hoffmann-La Roche Ltd) was used. The induction regimen consisted of 1000 mg intravenous injection, repeated once after 2 weeks. For the maintenance phase, 500-1000 mg was administered every 6 months, with the specific dose tailored to the patient's individual condition, disease control status, and tolerance. The infusion process required strict control of the rate. For the initial infusion, the starting infusion rate was 50 mg/h. After the first 60 minutes, the rate could be increased by 50 mg/h every 30 minutes, up to a maximum rate of 400 mg/h. For subsequent infusions, the starting rate of rituximab infusion could be 100 mg/h, increasing by 100 mg/h every 30 minutes, up to a maximum rate of 400 mg/h. Closely monitor patients' vital signs during injection.[19]

The administration method for Group B was subcutaneous injection, using Satralizumab Injection (Enspryng, SFDA registration number SJ20210017, F. Hoffmann-La Roche Ltd). The loading dose was subcutaneous injection given at week 0, 2, and 4, with a dose of 120 mg each time. After completing the three loading dose injections, a maintenance dose of 120 mg was administered every 4 weeks thereafter. The injection site could be the abdomen or thigh.[19]

Both groups of patients were treated for 18 months. During the treatment period, the patients' condition changes were closely observed, and the drug dose and treatment plan were adjusted according to the patients' specific conditions.

Observation indicators

Primary observation indicators

Annualized Relapse Rate (ARR)

The ARR of NMOSD is a core indicator for evaluating disease activity and treatment effectiveness. It refers to the average number of acute relapses meeting diagnostic criteria that occur annually in a patient population during a specific observation period. The lower the ARR, the more significant the effect of treatment in preventing relapses.

The calculation formula is as follows[20]:

ARR = number of relapses before or during drug therapy / total observation time.

The clinical definition of relapse (excluding symptom exacerbation caused by other reasons such as infection, metabolic abnormalities, etc.) usually includes (1) Optic neuritis relapse: acute or subacute onset of decreased vision, visual field defect, eye pain, etc., with or without optic nerve imaging abnormalities; (2) Myelitis relapse: limb weakness with acute or subacute onset, sensory abnormalities, bowel and bladder dysfunction, etc., accompanied by new or enhanced lesions on spinal cord imaging; (3) Brainstem/ Diencephalic syndrome relapse: such as acute vertigo, vomiting, drowsiness, body temperature accommodation abnormal.[21] The time frame for relapses before drug therapy is within 12 months prior to the initiation of treatment; the time frame for relapses during drug therapy ranges from the first administration of treatment to 18 months after the start of treatment.

Expanded Disability Status Scale (EDSS) Score

The EDSS is a frequently employed tool to measure the severity of neurological disability in patients with NMOSD. It is based on the evaluation of eight functional systems of the central nervous system (pyramidal, cerebellar, brainstem, sensory, bowel and urinary bladder, visual, cerebrum, other). Scores span from 0 to 10, where a higher score corresponds to greater severity of neurological coloboma.[22]

Changes in AQP4-IgG concentration

5 mL of fasting venous blood was collected from patients in procoagulation tubes as test samples, and serum was separated after centrifugation

at 3000 r/min for 10 min using a Beckman Microfuge® 20R centrifuge. Human AQP-4 Ab ELISA Kit (sensitivity: 0.39 ng/mL, CSB-E13568h, Cusabio) was used for AQP4-IgG detection.

Treg and CD20+ B cell count

5 mL of fasting venous blood was collected from patients in anticoagulant tubes as test samples, and Treg and CD20+ B cell count were performed using a BD FACSAria™ Fusion flow cytometer.

Secondary observation indexes

Levels of inflammatory factors and IgG subclasses

Serum collection method is the same as in 2.6.1.3. IL-6 was detected using Human IL-6 ELISA KIT (sensitivity: 2.453 pg/mL, CSB-E04638h, Cusabio); TNF-α was detected using Human TNF-α ELISA KIT (sensitivity: 1.95 pg/mL, CSB-E04740h, Cusabio); IgG1 was detected using Human IgG1 ELISA Kit (sensitivity: 50 pg/mL, EHIGG1, Invitrogen); IgG3 was detected using Human IgG3 ELISA Kit (sensitivity: 0.21 ng/mL, BMS2094, Invitrogen).

Adverse reaction events

Adverse reaction events that occurred in seropositive NMOSD patients treated with rituximab and satralizumab included infection, infusion/injection reactions, immunisation cell effects, and hepatic function abnormal, etc.[23]

Quality of Life Score (SF-36)

Internationally, the SF-36 serves as a tool for assessing health-related quality of life, which is widely used in the comprehensive evaluation of the treatment effect of chronic diseases (such as NMOSD). It contains a total of 36 items, and comprehensively assesses patients' physical and mental health status from 8 dimensions: physical functioning (PF), role-physical (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role-emotional (RE), and mental health (MH). The score range of each dimension is 0-100 points, and the higher the score, the better the function of the dimension[24]. This study mainly evaluated GH.

Sample size calculation

The sample size selection was based on a rigorous analysis using G*Power 3.1.9.7 statistical software to determine the sample size required to detect statistically significant differences. With the α value set at 0.05 and the test efficacy at 80%, the effect size (*Cohen's d*) was estimated to be 0.68 based on the literature (rituximab ARR of 0.25[22] and satralizumab ARR of 0.12[25]), and the calculation resulted in 35 cases per group. Considering potential loss to follow-up or data deletion (10%-15%), expanding to 40-60 cases per group can improve the stability of the results. The final analyzed data in this study were 60 cases in Group A and 62 cases in Group B, exceeding the statistical requirements, which can ensure the reliability of the results.

Statistical methods

SPSS 26 software was used for statistical analysis of the data. For data such as ARR, EDSS, antibody levels, inflammatory factor levels, and some baseline information of patients, if they conform to a normal distribution, they are expressed as $\pm s$. *Independent samples t-test* are selected for comparisons between groups, and *paired t-test* are used for before-and-after treatment comparisons within the same group. Non-normally distributed measurement data are expressed as *median (interquartile range)* [*M(IQR)*], and the *Mann-Whitney U test* is used for comparisons between groups. For categorical count data such as adverse reaction events and some baseline information, they are presented as *n (%)*, and group comparisons are performed using the *chi-square test*. A $P<0.05$ was considered to indicate a statistically significant difference. Recurrence time was analyzed using Kaplan-Meier curves. Between-group comparisons were unadjusted; no multivariable regression, propensity-score methods, or inverse-probability weighting were performed, so results reflect crude associations.

- No multivariate adjustment or propensity score matching was performed. Therefore, all between-group comparisons represent unadjusted associations only, even though statistically significant differences exist.

RESULTS

Comparison of baseline information between the two groups

Table 1 illustrates the baseline data of the patients. In this retrospective array, the baseline information of patients included age, BMI,

gender, course, history of hypertension, history of diabetes mellitus, history of thyroid disorder, history of previous infection, type of first onset, prior exposure to immunosuppressants, treatment status, duration of disease, number of prior attacks, current treatment duration, ARR EDSS scores and background drugs. Comparing Group A and Group B, baseline data suggested no significant differences between the two groups (all $P>0.05$), signifying that the two groups of patients had good comparability before treatment. In this study, the pre-treatment indicators are defined by type: (1) Baseline characteristics: from disease onset to the start date of treatment; (2) Observation indicators: within 12 months before the start date of treatment. This definition is followed in all subsequent sections.

Comparison of ARR between the two groups of patients

The analysis of data results, as displayed in Table 2 and Figure 2, indicates that no significant difference was found in ARR before treatment between Group A (0.99±0.26 per person-year) and Group B (0.99±0.25 per person-year) (*95%CI*: -0.10-0.09, $P=0.911$). Relative to before treatment, the ARR of both groups exhibited a statistically significant reduction following treatment (all $P<0.05$). It can also be seen that after treatment, the ARR observed in Group B was statistically lower than that of Group A (0.25±0.12 per person-year vs. 0.20±0.13 per person-year, *95%CI*: 0.003-0.09, $P=0.035$). The median recurrence time was 12.11 months (*95% CI*: 9.89–14.33) in Group A and 14.89 months (*95% CI*: 13.63–16.15) in Group B. The recurrence time in Group B was statistically longer than that in Group A [*HR*: 1.77 (1.16, 2.72), $P=0.006$] (Figure 3). From these data analyses, it can be concluded that both satralizumab and rituximab are association with reducing recurrence in serum-positive NMOSD patients, and satralizumab is associated with greater change than rituximab.

Comparison of EDSS scores between the two groups of patients

The analysis of the data in Table 2 and Figure 4 suggests that there was no significant difference in EDSS scores between the two groups of patients before treatment (3.98±1.85 scores vs. 4.05±1.89 scores) (*95%CI*: -0.74-0.61, $P=0.848$). Following treatment, a statistically significant reduction in EDSS scores was observed in patients from both groups (all $P<0.05$), indicating that both antibody treatments are association with disease remission. In addition, compared with Group A (2.50±0.97 scores) after treatment, the EDSS score of Group B (2.15±0.99 scores) suggested decreased statistically lower (*95%CI*: 0.004-0.7, $P=0.047$), indicating that satralizumab was associated with more significant improvement in nerve function and recovery of the condition compared with the use of rituximab.

Comparison of AQP4-IgG concentrations between the two groups

Analyzing the AQP4-IgG concentrations in Table 2, from this, it logically follows that the concentration levels of the two patient groups did not differ statistically significant before treatment (100.16±27.04 ng/mL vs. 100.19±26.59 ng/mL), indicating that the two patient groups were suitable for comparison (*95%CI*: -9.65-9.58, $P=0.994$). After treatment, the AQP4-IgG concentrations in either group statistically decreased (all $P<0.05$), and the concentration in Group A (50.85±5.26 ng/mL) was more statistically significant lower than that in Group B (53.98±10.60 ng/mL) (*95%CI*: -6.13--0.14, $P=0.040$). Based on these data, both rituximab and satralizumab were associated with reductions in AQP4-IgG concentrations and clinical improvement, with rituximab showing a greater effect on AQP4-IgG reduction.

Comparison of Tregs and CD20+ cells between the two groups of patients

The data in Table 2 analyzed two types of immunisation cells. It was found that there were no significant difference in Treg (110.37±5.22 cells/μL vs. 110.21±5.24 cells/μL) and CD20+ counts (350.37±5.22 cells/μL vs. 349.89±6.10 cells/μL) before treatment (*95%CI*: -1.72-2.03, $P=0.869$; *95%CI*: -1.56-2.52, $P=0.642$). After treatment, Treg was statistically increased in both groups (all $P<0.05$), CD20+ was statistically decreased in Group A ($P<0.05$), and there was no significant change in CD20+ in Group B ($P>0.05$). In addition, compared with the number of Treg cells in Group A (182.55±10.69 cells/μL), the increase in Group B was more significant (*95%CI*: -8.77--1.17, $P=0.011$); compared with the number of CD20+ in Group B (350.31±7.26 cells/μL), the decrease in Group A (110.15±5.15 cells/μL) was more significant (*95%CI*: -242.42--237.89, $P<0.001$). These data suggest that

Table 1: Baseline characteristics [$\bar{x}\pm s$, *n (%)*]

Variables	Group A (n=60)	Group B (n=62)	*95%CI*		*P*	*Effect size*
			Lower	*Upper*		
Age (years)	57.55±10.69	58.06±8.94	-4.04	3.01	0.773	-0.05
BMI (kg/m2)	24.02±1.59	23.50±1.72	-0.07	1.12	0.083	0.31
Gender						
Male	33 (55)	34 (54.8)	0.49	2.05	0.986	0.002
Female	27 (45)	28 (45.2)				
Course of disease (months)	49.00±11.03	48.55±11.15	-3.52	4.43	0.822	0.04
Hypertension	26 (43.3)	27 (43.5)	0.48	2.03	0.981	-0.002
Diabetes	15 (25)	19 (30.6)	0.34	1.67	0.487	-0.06
Disease of thyroid gland	12 (20)	13 (21.0)	0.39	2.27	0.895	-0.01
Infectious history	8 (13.3)	9 (14.5)	0.33	2.53	0.85	-0.02
First-onset type						
Optic neuritis	36 (60)	37 (59.7)	-	-	0.996	0.008
Myelitis	18 (30)	19 (30.6)				
Brainstem syndrome	6 (10)	6 (9.7)				
Prior exposure to immunosuppressants						
Mycophenolate mofetil	12 (20.0)	13 (21.0)	-	-	0.992	0.019
Azathioprine	7 (11.7)	8 (12.9)				
Cyclophosphamide	2 (3.3)	2 (3.2)				
Treatment status						
First-line treatment	39 (65.0)	39 (62.9)	0.52	2.30	0.809	0.022
Non-first-line treatment	21 (35.0)	23 (37.1)				
Duration of disease (months)	16.75±7.84	16.73±8.30	-2.87	2.92	0.987	0.003
Number of prior attacks	3.60±1.28	3.52±1.30	-0.38	0.55	0.720	0.065
Current treatment duration (months)	26.20±5.05	25.19±4.55	-0.72	2.73	0.250	0.21
ARR (per person-year)	0.99±0.26	0.99±0.25	-0.10	0.09	0.911	<0.001
EDSS scores	3.98±1.85	4.05±1.89	-0.74	0.61	0.848	-0.04
Background drugs						
AZA	28	25			0.480	0.064
MMF	15	17			0.761	-0.027
Steroid tapers	30	33			0.722	-0.032
Plasmapheresis and IVIG	6	4			0.475	0.065

Note: BMI: body mass index; ARR: annual relapse rate; EDSS: expanded disability status scale; AZA: Azathioprine; MMF: Mycophenolate Mofetil; IVIG: Intravenous Immunoglobulin.

Table 2: Comparison of primary observation indicators ($\bar{x}\pm s$)

Variables	Time	Group A (n=60)	Group B (n=62)	*95%CI*		*P*	*Effect size*
				Lower	*Upper*		
ARR (per person-year)	Before treatment	0.99±0.26	0.99±0.25	-0.10	0.09	0.911	<0.001
	After treatment	0.25±0.12*	0.20±0.13*	0.003	0.09	0.035	0.40
EDSS score (scores)	Before treatment	3.98±1.85	4.05±1.89	-0.74	0.61	0.848	-0.04
	After treatment	2.50±0.97*	2.15±0.99*	0.004	0.7	0.047	0.36
AQP4-IgG (ng/mL)	Before treatment	100.16±27.04	100.19±26.59	-9.65	9.58	0.994	-0.001
	After treatment	50.85±5.26*	53.98±10.60*	-6.13	-0.14	0.040	-0.373
Treg (cells/μL)	Before treatment	110.37±5.22	110.21±5.24	-1.72	2.03	0.869	0.03
	After treatment	182.55±10.69*	187.52±10.51*	-8.77	-1.17	0.011	-0.47
CD20+ (cells/μL)	Before treatment	350.37±5.22	349.89±6.10	-1.56	2.52	0.642	0.08
	After treatment	110.15±5.15*	350.31±7.26	-242.42	-237.89	<0.001	-38.16

Note: *P<0.05 vs. before treatment; AQP4-IgG: aquaporin 4-immunoglobulin G; Treg: regulatory T cells; CD20+: cluster of differentiation 20.

both rituximab and satralizumab increased Treg counts and enhanced immune tolerance, with satralizumab showing a trend toward greater effect, while rituximab can numerically reduce B cell activation, but satralizumab has no obvious effect in this regard.

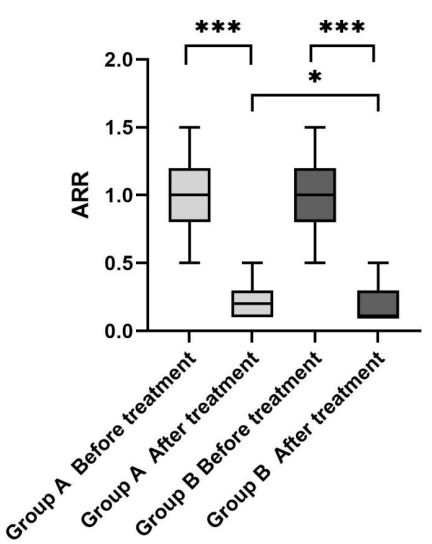

Figure 2. Comparison of ARR of patients

Comparison of inflammatory factor levels between the two groups

The data in Figure 3 mainly analyzed two inflammatory factors. There were no significant difference in IL-6 (42.22±3.25 ng/L vs. 42.34±3.29 ng/L) and TNF-α (39.75±9.22 ng/L vs. 39.95±9.14 ng/L) between the two groups before treatment, indicating good comparability (*95%CI*: -1.29-1.05, *P*=0.842; *95%CI*: -3.49-3.09, *P*=0.903). After treatment, both inflammatory factors were statistically reduced (all *P*<0.05), and compared to Group A (23.13±1.71 ng/L; 18.93±8.69 ng/L), these two inflammatory factors in Group B (22.10±1.85 ng/L; 15.41±10.13 ng/L) was more statistically lower (*95%CI*: 0.39-1.66, *P*=0.002; *95%CI*: 0.13-6.91, *P*=0.042). The above results indicate that both treatments were associated with reductions in inflammatory markers, with satralizumab demonstrating a greater trend in this regard.

Comparison of IgG subclass levels between the two groups

Table 3 analyzes two IgG subclasses. There were no significant differences in IgG1 (1105.73±4.92 mg/dL vs. 1105.90±4.93 mg/dL) and IgG3

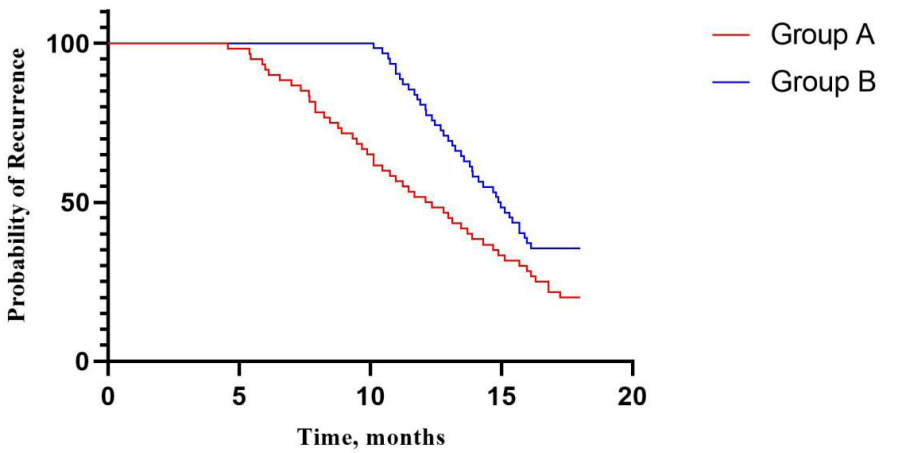

Figure 3. Comparison of recurrence time of patients

(110.37±5.22 mg/dL vs. 110.21±5.24 mg/dL) between the two groups before treatment (*95%CI*: -1.94-1.60, *P*=0.849; *95%CI*: -1.72-2.03, *P*=0.869). After treatment, IgG1 and IgG3 were statistically decreased (all *P*<0.05), and compared with Group B (599.89±6.10 mg/dL; 59.00±5.24 mg/dL), these two IgG subclasses in Group A (596.92±5.15 mg/dL; 57.10±5.32 mg/dL) was more significant lower (*95%CI*: -5.00--0.94, *P*=0.004; *95%CI*: -3.80--0.02, *P*=0.048). The above results indicate that rituximab and satralizumab are associated with reducing body fluid immunisation in patients, and rituximab has a greater trend in this regard.

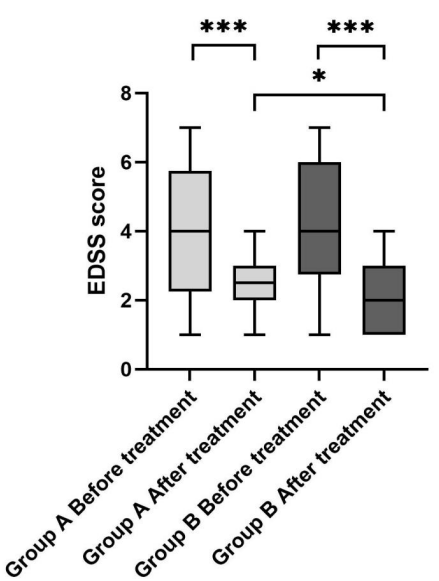

Figure 4. Comparison of EDSS score of patients

Comparison of SF-36-GH scores between the two groups

Scores for the overall health status of the two patient groups were obtained, and these are illustrated in Table 3. Before treatment, SF-36-GH scores did not differ statistically between the two groups (49.00±11.03 scores vs. 48.55±11.15 scores, *95%CI*: -3.52-4.43, *P*=0.822). After treatment, the SF-36-GH scores of both groups of patients increased statistically (all *P*<0.05), indicating that both drugs improved the health status of the patients. It can also be seen that SF-36-GH scores in Group B was more statistically higher compared with Group A (59.68±11.07 scores vs. 63.69±11.07 scores, *95%CI*: -7.98--0.04, *P*=0.048). This suggests that satralizumab treatment is associated with greater change than rituximab in improving the health status of patients.

Comparison of adverse event incidence between the two groups

As shown in Table 4, in Group A, there were 8 cases of infection, 9 cases of infusion/injection reactions, and 4 cases of immune cell effects, with a total adverse reaction event incidence of 35%. In Group B, there were 2 cases of infection, 2 cases of infusion/injection reactions, 6 cases of immune cell effects, and 2 cases of liver dysfunction, with a total adverse event incidence

Table 3: Comparison of secondary observation indexes ($\bar{x}\pm s$)

Variables	Time	Group A (n=60)	Group B (n=62)	95%CI		*P*	*Effect size*
				Lower	*Upper*		
IL-6 (ng/L)	Before treatment	42.22±3.25	42.34±3.29	-1.29	1.05	0.842	-0.04
	After treatment	23.13±1.71*	22.10±1.85*	0.39	1.66	0.002	0.58
TNF-α (ng/L)	Before treatment	39.75±9.22	39.95±9.14	-3.49	3.09	0.903	-0.02
	After treatment	18.93±8.69*	15.41±10.13*	0.13	6.91	0.042	0.37
IgG1 (mg/dL)	Before treatment	1105.73±4.92	1105.90±4.93	-1.94	1.60	0.849	-0.03
	After treatment	596.92±5.15*	599.89±6.10*	-5.00	-0.94	0.004	-0.53
IgG3 (mg/dL)	Before treatment	110.37±5.22	110.21±5.24	-1.72	2.03	0.869	0.03
	After treatment	57.10±5.32*	59.00±5.24*	-3.80	-0.02	0.048	-0.36
SF-36-GH score	Before treatment	49.00±11.03	48.55±11.15	-3.52	4.43	0.822	0.04
	After treatment	59.68±11.07*	63.69±11.07*	-3.80	-0.02	0.048	-0.36

Note: *P<0.05 vs. before treatment; IL-6: interleukin-6; TNF-α: tumor necrosis factor-α; IgG1: immunoglobulin G1; IgG3: immunoglobulin G3; SF-36-GH: 36-item short form survey-general health.

of 19.4%. Overall adverse events suggested no significant differences (*95%CI*: 0.99-5.11, *P*=0.052), but the infusion/injection reactions and infection were significant differences (*95%CI*: 1.10-25.63, *P*=0.023; *95%CI*: 0.94-22.71, *P*=0.042). This indicates that no significant difference is observed in the incidence of adverse events between satralizumab and rituximab treatment, but rituximab has more adverse events were observed in terms of infusion/injection reactions and infection.

DISCUSSION

Seropositive NMOSD is an autoimmune disease of the central nervous system mediated by AQP4-IgG.[1] Traditional immunosuppressive agents have a slow onset of action. Therefore, there is an urgent clinical need for more efficient and safer targeted therapies. In recent years, with the deepening of research on the immunisation mechanism of NMOSD, the employment of biological agents has notably altered the treatment paradigm of this disease.[26] Among them, satralizumab and rituximab are two commonly used targeted therapies in clinical practice. The two drugs have different mechanisms of action, and there are also differences in their efficacy trait, safety profile, and clinically applicable populations.

Several randomized controlled trials and real-world investigations have demonstrated that both drugs can lead to a substantial reduction in the ARR in seropositive NMOSD patients. Barreras *et al*.[20] conducted a retrospective analysis of 111 NMOSD patients, the median duration of rituximab treatment was 3.7 years (0.5-13.2 years), and the ARR decreased (median ARR: 1.1 before treatment, 0 after treatment). Satralizumab in the SAkuraStar and SAkuraSky trials[27], the ARR during the 18-month treatment period was 0.05-0.2 per/person-year, a 70%-80% reduction compared to the placebo group; while the ARR of rituximab was 0.1-0.3 per/person-year, a 60%-70% reduction compared to traditional immunosuppressive agents (such as azathioprine), which is consistent with the changes in ARR of the two drugs in the results of this study. This difference is related to the

Table 4 : Comparison of adverse events of patients [*n (%)*]

Variables		Adverse events				
		Infection	**infusion/ injection reactions**	**immune cell effects**	**liver dysfunction**	**total**
Group A (n=60)		8 (13.3)	9 (15)	4 (6.7)	0 (0.0)	21 (35)
Group B (n=62)		2 (3.2)	2 (3.2)	6 (9.7)	2 (3.2)	12 (19.4)
95%CI	*Lower*	0.94	1.10	0.18	0.93	0.99
	Upper	22.7	25.63	12.49	1.01	5.11
P		0.042	0.023	0.544	0.154	0.052
Effect size		0.18	0.21	-0.06	0.13	0.18

drug's target. Satralizumab directly inhibits the initiation of the inflammatory cascade by blocking IL-6 signalling, thereby rapidly controlling acute inflammation; rituximab, on the other hand, depletes CD20+ B cells to reduce the production of AQP4-IgG, focusing more on long-term prevention of antibody-mediated relapse. The EDSS score is a core indicator for assessing neurological disability in NMOSD patients. In a retrospective chart review and analysis of 108 patients using low-dose rituximab by Zhao *et al*.[28], the EDSS score decreased (3.5 vs. 2.0). Meta-analyses[29] have suggested that both satralizumab and rituximab can reduce EDSS scores in NMOSD patients, which is similar to the EDSS changes in this study. This difference may be explained by the possible effects of IL-6 blockade in limiting neuroinflammation and preserving tissue integrity, whereas B-cell depletion primarily targets antibody-mediated injury and may have less influence on acute inflammatory pathways.[30] The overall health score in the SF-36 quality of life further supports this difference: the satralizumab group improved by 15-20 points, and the rituximab group improved by 10-15 points, suggesting that satralizumab is more advantageous in improving patients' quality of life and health, possibly due to its rapid relief of inflammation-related symptoms such as fatigue and pain.[31]

Satralizumab has no effect on CD20+ cells. While its effects on AQP4-IgG and IgG1 appear less pronounced compared to rituximab, these data suggest that satralizumab may show a stronger trend toward immune tolerance, particularly in its effects on the pro-inflammatory cytokines IL-6 and TNF-α.[32] CD4+ T cell subset loss of balance is a core trait of NMOSD immune dysregulation. As a part of CD4+ cells, Treg cells have immunosuppression effects and can inhibit the immune response of other immune cells. They are the main controllers of self-tolerance. Satralizumab numerically increases the number of Treg cells; rituximab has a weaker effect on T cell subsets compared to satralizumab. It is possible that this difference stems from the fact that IL-6 plays a key role in Th17 differentiation, and that the blockade of IL-6 signalling by satralizumab may directly promote Treg proliferation and inhibit Th17 activation. Hao Wang *et al*.[33] included 36 studies for analysis. The rates of infusion-related adverse events, infections, respiratory and urinary tract infections in patients receiving treatment with rituximab were 28.57%, 5.66%, 27.01%, 17.36%, 4.76%, and 4.76%, respectively. The risk ratio of developing any infection (1.24, *95%CI*: 0.18-8.61) bore a resemblance to azathioprine's. Yamamura *et al*.[34] conducted a post-marketing clinical surveillance study in 570 patients treated with satralizumab, and 28 patients (4.91%) developed infections, with no infusion-related adverse events observed. These data are consistent with the findings in this study, suggesting that satralizumab may show a stronger trend toward immune tolerance, as it is associated with a lower rate of infection and infusion-related adverse events compared to rituximab. This may be because rituximab infusion reactions are mainly attributed to its immunogenicity and the release of cytokines, while the increased risk of infection may be directly related to the humoral immune defect and impaired antigen presentation function caused by long-term B-cell depletion. In contrast, satralizumab only blocks the IL-6 signalling pathway and has no direct destructive effect on B cells, which may contribute to its lower rates of

infusion reactions and infection. This may also represent a core difference between the two in terms of safety profile.

This study has the following limitations. This study is a retrospective study. Although the data collection and analysis were completed by researchers who were not involved in patient treatment, which ensured the objectivity of the research to some degree, the retrospective study itself has certain limitations. The influence of confounding factors cannot be completely excluded. Moreover, this study included 122 patients, all of whom were admitted to our hospital. While they satisfy the fundamental statistical criteria, the sample size is relatively small and does not cover groups with different economic levels and cultural backgrounds. There may be selection bias, and the universality and representativeness of the research results are affected to a certain extent. In addition, the sample size for special subgroups (such as AQP4-IgG ultra-high titre, combined with multi-organ autoimmune diseases, elderly patients) is insufficient. On the other hand, the duration of this study was 18 months, lacking long-term data of more than 5 years. The analysis of immune cell subgroups in this study was mostly limited to basic indicators (such as CD20+ B cell count, Treg cell count), lacking in-depth exploration of refined subgroups (such as Tfh cells, memory B cell subgroups, dynamic changes in cytokine networks), Moreover, the indicator CD19+ was not analyzed, and this limitation may have a slight impact on the assessment of the degree of B-cell depletion after rituximab treatment. Going forward, multi-center, large-sample, prospective randomized controlled trials can be conducted to expand the research sample size, include patients from different regions and different living backgrounds, combine precise immunisation detection technologies (such as single-cell sequencing, multi-omics analysis) to improve the universality and reliability of the research results, and use CD19+ as the core indicator for B-cell monitoring after rituximab treatment to more accurately assess the regulatory effect of treatment on B cells. At the same time, long-term follow-up (3-5 years) should be conducted, and stratified random design should be performed to more comprehensively reveal the differences between the two drugs and provide a more solid evidence for individualized treatment.

In conclusion, in this retrospective, single-center cohort, satralizumab and rituximab demonstrated different clinical and immunologic profiles. Satralizumab was associated with lower ARR and EDSS at 18 months and with reductions in inflammatory markers, while rituximab produced greater $CD20^{+}$ B-cell depletion. Given the unadjusted analyses, single-center design, and limited follow-up, these findings are hypothesis-generating and should not be interpreted as definitive comparative efficacy. Multicenter, prospective head-to-head trials are required to establish comparative effectiveness and safety.

DISCLOSURE

Ethics: This study was approved by the Ethics Committee of The Second Hospital of Lanzhou University. We secured a signed informed consent form from every participant.

Data availability: The data that support the findings of this study are available from the corresponding author, upon reasonable request.

Financial support: None

Conflicts of interest: None

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