Original research

Early rituximab treatment reduces long-term disability in aquaporin-4 antibody-positive neuromyelitis optica spectrum

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ABSTRACT

Background Neuromyelitis optica spectrum disorder (NMOSD) causes relapsing inflammatory attacks in the central nervous system, leading to disability. As rituximab, a B-lymphocyte-depleting monoclonal antibody, is an effective in preventing NMOSD relapses, we hypothesised that earlier initiation of rituximab can also reduce long-term disability of patients with NMOSD.

Methods This multicentre retrospective study involving 19 South Korean referral centres included patients with NMOSD with aquaporin-4 antibodies receiving rituximab treatment. Factors associated with the long-term Expanded Disability Status Scale (EDSS) were assessed using multivariable regression analysis.

Results In total, 145 patients with rituximab treatment (mean age of onset, 39.5 years; 88.3% female; 98.6% on immunosuppressants/oral steroids before rituximab treatment; mean disease duration of 121 months) were included. Multivariable analysis revealed that the EDSS at the last follow-up was associated with time to rituximab initiation (interval from first symptom onset to initiation of rituximab treatment). EDSS at the last follow-up was also associated with maximum EDSS before rituximab treatment. In subgroup analysis, the time to initiation of rituximab was associated with EDSS at last follow-up in patients aged less than 50 years, female and those with a maximum EDSS score ≥6 before rituximab treatment.

Conclusions Earlier initiation of rituximab treatment may prevent long-term disability worsening in patients with NMOSD, especially among those with early to middle-age onset, female sex and severe attacks.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Rituximab, a monoclonal antibody against CD20, is an effective treatment option to prevent relapses in neuromyelitis optica spectrum disorder (NMOSD). However, it is still unclear if earlier initiation of rituximab treatment will lead to a better long-term disability outcome for patients with NMOSD, and also which patients will be more benefited with early rituximab treatment.

WHAT THIS STUDY ADDS

⇒ Initiating rituximab treatment sooner after symptom onset was significantly linked to better long-term disability outcomes in patients with NMOSD. This effect was more pronounced in patients under 50 years old, females and those with a maximum Expanded Disability Status Scale before rituximab ≥6.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Patients with NMOSD who experience breakthrough relapses, especially those with early to middle-age onset, female sex and severe attacks, need to be switched to rituximab treatment in their early disease stages.

INTRODUCTION

Neuromyelitis optica spectrum disorder (NMOSD) is an inflammatory disease of the central nervous system, predominantly characterised by optic neuritis and longitudinally extensive transverse myelitis.[1 2] The discovery of a disease-specific autoantibody against aquaporin-4 (AQP4) identifies NMOSD as a disorder that is distinct from multiple sclerosis (MS)[3] and also suggests that B cell-mediated immune mechanisms play a pivotal role in NMOSD.[4 5]

Various immunosuppressive agents, including azathioprine, methotrexate, cyclophosphamide and mycophenolate mofetil, have been widely used to achieve clinical remission and prevent recurrence.[1 6 7] Recently, the Food and Drug Administration (FDA) approved eculizumab (complement C5 inhibitor),[8] satralizumab (interleukin-6 receptor inhibitor),[9] and inebilizumab (targeting CD19-expressing B-cells)[10] for treating NMOSD.

In addition to the aforementioned FDA-approved treatments, rituximab, a monoclonal

antibody against CD20, has long been used to prevent relapses of NMOSD[1 7 11] and was recently proved to be a potent treatment option in several clinical trials.[2 6 12]

As the majority of patients with NMOSD have a relapsing disease course without secondary progression, prevention of relapse in NMOSD can be crucial in preventing long-term accumulation of disability. Treatment with rituximab is associated with the prevention of relapses in NMOSD[11 13]; however, the effect of earlier use of rituximab on long-term disability in NMOSD has not been clearly demonstrated. Several recent studies advocate the earlier initiation of high-efficacy disease-modifying therapies in MS with poor prognostic factors,[14 15] but this approach has not yet been clearly evaluated in NMOSD. We aimed to evaluate the effect of early rituximab treatment on long-term disability in patients with NMOSD.

METHODS

Participants

Nineteen tertiary referral hospitals in South Korea participated in this multicentre retrospective study. The inclusion criteria were (1) diagnosis of NMOSD according to the international consensus diagnostic criteria in 2015,[16] (2) history of rituximab treatment and (3) follow-up period of more than 1 year.

A total of 151 patients were tested for AQP4 antibody, and among them 67 patients were also tested for myelin oligodendrocyte glycoprotein (MOG) antibody. Six patients were double positive for AQP4 and MOG antibody and excluded, because of the distinct clinical features of MOG antibody disorders from those of AQP4 antibody-positive NMOSD.[17] Finally, 145 patients were included.

Clinical measurements

The medical records of patients' demographic and clinical parameters, including age, sex, body mass index, serologic status (AQP4 antibody), date of symptom onset (first attack), combined autoimmune disease (eg, Sjogren's syndrome or systemic lupus erythematosus), location of first attack (brain, spinal cord or optic nerve), maximal length of spinal cord lesion, date of last follow-up, number of attack before rituximab treatment, disease course (relapsing or monophasic) were reviewed.

The parameters of severity, including presence of severe optic neuritis (visual acuity <0.1, at optic neuritis nadir), degree of impairment in gait, maximum Expanded Disability Status Scale (EDSS) before rituximab, EDSS at last follow-up,[18] and parameters of treatment, including rituximab therapy regimen (date of rituximab start, total number of infusions, induction regimen and maintenance regimen), dose of combined corticosteroid, plasmapheresis before rituximab and adverse effects, were also reviewed. EDSS scores were assessed at each clinical attack and regular outpatient visits. The 'maximum EDSS before rituximab' represent that the worst EDSS score at clinical attacks before rituximab treatment. Relapse was defined as the worsening of new neurological symptoms that lasted at least 24 hours.[1 11] The time to initiation of rituximab was defined as the interval from first symptom onset to initiation of rituximab treatment.

We defined the EDSS at the last follow-up as the main efficacy indicator[19] and analysed the factors affecting an EDSS≥6 at the last follow-up, which indicates a poor prognosis with severe disability.

Table 1 Characteristics of patients with NMOSD treated with rituximab

	Patients (n=145)
Age at disease onset (years)	39.5±13.4 (7–72 years)
Sex	
Female	128 (88.3%)
Male	17 (11.7%)
Serology	
Anti-AQP4 antibody positive	135 (93.1%)
Anti-AQP4 antibody negative	10 (6.9%)
Disease duration (months)	120.6±132.4
BMI (kg/m^2)	22.7±3.5
Location of first attack	
Brain	30 (20.7%)
Spinal cord	47 (32.4%)
Optic nerve	61 (42.1%)
Multifocal location	7 (4.8%)
Time to initiation of rituximab (months)*	77.1±80.6 (0–372 months)
Concomitant autoimmune disease	37 (25.5%)
Ambulation without assistance at initiation of rituximab	88 (60.7%)
Severe ON†	57 (39.3%)
Previous treatments	
Naïve	0
MS medication only	2 (1.4%)
Immunosuppressants and interferon	9 (6.2%)
Immunosuppressants and immunoglobulin	1 (0.7%)
Oral steroid only	26 (17.9%)
Other immunosuppressants (with or without oral steroid)	106 (73.1%)
Unknown	1 (0.7%)
EDSS	
Maximum EDSS before rituximab	5.2±2.2 (1–9.5)
EDSS at last follow-up	3.0±2.5 (0–9.5)
Disease course (monophasic vs relapsing)	1:144 (0.7:99.3%)
No of attacks before rituximab	5.03±3.93
No of attacks after rituximab	0.53±1.24
Relapse-free patients after rituximab	105 (72.4%)
Cumulative no of rituximab infusion	6.8±4.2
Dosage of concomitant oral steroid at initiation of rituximab (mg/day)	24.4±90.4
Patients with plasmapheresis treatment before initiation of rituximab	75 (51.7%)
Treatment duration of rituximab (months)	31.65±31.25
Rituximab treatment regimen	
Induction	
375 mg/m^2 infused weekly for 4 weeks	87 (60%)
1000 mg infused twice at 2-week interval	46 (31.7%)
Others	11 (7.6%)
U/C	1 (0.7%)
Maintenance	
Fixed time points infusion‡	38 (26.2%)
Infusion based on CD19 or CD 27 counts	97 (66.9%)
Other	9 (6.2%)
Unknown	1 (0.7%)

Results are presented as mean±SD or n (%).
*Time to initiation of rituximab: interval from first symptom onset to initiation of rituximab treatment.
†Severe ON: visual acuity <0.1, ON nadir.
‡Fixed time-points infusion: for example, every 6–12 months.
AQP4, aquaporin-4; BMI, body mass index; EDSS, Expanded Disability Status Scale; MS, multiple sclerosis; NMOSD, neuromyelitis optica spectrum disorder; ON, optic neuritis; U/C, uncheckable.

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics V.25.0 (IBM). Linear and logistic regression analyses were performed to assess factors associated with EDSS at the last follow-up and severe disability defined as a final EDSS≥6, respectively. As each patient had a different follow-up duration,

the EDSS at the last follow-up was measured at different disease statuses. To minimise the effect of each patient's follow-up duration on their EDSS at the last follow-up, all variables were adjusted by the duration of follow-up, defined as the interval from initiation of rituximab to the date of final EDSS measurement. All variables with p<0.05 on univariable analysis were included in the multivariable analysis. Because of the severe multicollinearity between plasmapheresis and maximum EDSS before rituximab, we have not included plasmapheresis which was not significant when adjusted for maximum EDSS before rituximab in a multivariable linear and logistic regression model (online supplemental tables E1 and E2). After the initial analysis, a subgroup analysis was performed to assess which patients had a more favourable outcome with early rituximab treatment.

RESULTS

Patient characteristics

Initially, 151 patients with NMOSD with a history of rituximab treatment from 19 referral centres were screened; among them, 6 were excluded because of positive MOG antibody test results. In total, 145 patients with NMOSD (93.1% AQP4 antibody-positive) were included.

All of enrolled patients have received various immunosuppressants including oral steroid (n=116), azathioprine (n=76), mycophenolate mofetil (n=56), interferon beta (n=11), cyclophosphamide (n=3), mitoxantrone (n=6) as their first-line treatment. Two patients have received teriflunomide, interferon and glatiramer acetate because they were initially misdiagnosed with MS. Concomitant steroid (n=52) and/or immunosuppressants (n=17) were also used during rituximab treatment in 62 patients. The mean±SD of maximum EDSS before rituximab was 5.2±2.2 and EDSS at the last follow-up was 3.0±2.5. Reinfusion of rituximab as maintenance regimen was performed when the CD19+ cells were at least 1% of peripheral blood mononuclear cells (n=90). Baseline characteristics of the study population are shown in table 1. Recorded adverse effects related to rituximab were: infusion related symptoms (rash, urticaria, throat irritation, fever, nasal congestion, laryngospasm, chest discomfort), n=12; respiratory infection, n=4; urinary tract infection, n=2; zoster infection, n=2; and others(anorexia, diarrhoea, vaginal bleeding, interstitial lung disease, colitis), n=5. There were no patients developing malignancy or progressive multifocal leukoencephalopathy during the rituximab treatment.

Factors associated with EDSS at the last follow-up

Univariable linear regression analysis revealed that the maximum EDSS before rituximab, number of attack before start of rituximab, time to initiation of rituximab and ambulation without assistance at initiation of rituximab were significantly associated with EDSS at the last follow-up. On multivariate analysis, the time to initiation of rituximab (p<0.001) was significantly associated with EDSS at the last follow-up (regression coefficient, 0.135 per year; 95% CI 0.07 to 0.20; p<0.001) along with maximum EDSS before rituximab (p<0.001) (table 2).

In subgroup analysis, the time to initiation of rituximab was a significant determinant factor for EDSS at the last follow-up in patients <50 years old at disease onset (p<0.001), in women (p<0.001), and in patients with a maximum EDSS≥6 before rituximab treatment (p<0.001) (table 3).

Table 2 Factors affecting the EDSS at last follow-up in patients with NMOSD treated with rituximab

	Univariable			Multivariable		
Characteristics	Coefficient	95% CI	P value	Coefficient	95% CI	P value
Sex (male)	0.090	−1.300 to 1.481	0.898			
BMI (per 1 kg/m^2)	0.088	−0.047 to 0.223	0.198			
Onset age (per year)	−0.001	−0.035 to 0.032	0.951			
AQP4-Ab positivity	0.625	−1.001 to 2.250	0.448			
Maximum EDSS before rituximab	0.664	0.492 to 0.837	<0.001	0.567	0.272 to 0.863	**<0.001**
Concomitant autoimmune disease	−0.141	−1.180 to 0.898	0.788			
No of attack before start of rituximab	0.197	0.090 to 0.304	<0.001	0.075	−0.040 to 0.191	0.199
Time to initiation of rituximab (per year)*	0.153	0.087~0.218	<0.001	0.135	0.070 to 0.199	**<0.001**
Location of first attack	0.195	−0.209 to 0.599	0.342			
Maximal length of spinal cord lesion	0.070	−0.014 to 0.153	0.101			
Severe ON	0.789	−0.097 to 1.674	0.080			
Ambulation without assistance at initiation of rituximab	2.536	1.759 to 3.313	<0.001	−0.033	−1.346 to 1281	0.961
Total infusion no of rituximab	0.030	−0.118 to 0.177	0.689			
Dose of combined steroid at initiation of rituximab (mg)	−0.001	−0.006 to 0.003	0.587			
Plasmapheresis before rituximab†	1.163	0.313 to 2.014	0.008			
Rituximab induction‡	−0.220	−0.916 to 0.477	0.533			
Continued rituximab treatment till last follow-up	−0.955	−2.275 to 0.365	0.154			
Rituximab maintenance§	0.242	−0.582 to 1.065	0.562			

P-value < 0.05 on multivariate analyis appears as bold

*Time to initiation of rituximab: interval from first symptom onset to initiation of rituximab treatment.

†Plasmapheresis before rituximab was not included in the multivariable linear regression model because of severe multicollinearity between plasmapheresis before rituximab and maximum EDSS score before rituximab and non-significance (coefficient=0.26 (0–0.52, 1.05), p=0.508) when adjusted for maximum EDSS score before rituximab (online supplemental table E1).

‡Rituximab induction regimen was classified into three categories: (1) 375 mg/m^2 infused weekly for 4 weeks (reference category), (2) 1000 mg infused twice at 2-week interval and (3) other.

§Rituximab maintenance regimen was classified into three categories: (1) fixed time points infusion (reference category), (2) infusion based on CD19 or CD27 counts and (3) other.

AQP4-Ab, aquaporin-4 antibody; BMI, body mass index; EDSS, Expanded Disability Status Scale; NMOSD, neuromyelitis optica spectrum disorder; ON, optic neuritis.

Table 3 Beneficial effect of early rituximab treatment was found in subgroups with young age, female gender and experience of high disability before rituximab

	Coefficient	95% CI	P value	P value for interaction
Onset age				
<50 (n=100)	0.013	0.007 to 0.019	<0.001	0.236
≥50 (n=35)	0.004	−0.011 to 0.018	0.644	
Sex				
Female (n=128)	0.011	0.006 to 0.017	<0.001	0.797
Male (n=17)	0.013	−0.002 to 0.028	0.083	
Maximum EDSS before rituximab				
<6 (n=66)	0.007	−0.002 to 0.016	0.105	0.227
≥6 (n=58)	0.014	0.007 to 0.020	<0.001	

CI, confidence interval; EDSS, Expanded Disability Status Scale; NMOSD, neuromyelitis optica spectrum disorder.

Logistic regression analysis for factors associated with severe disability (EDSS≥6 at the last follow-up) was also performed, and the time to initiation of rituximab (OR 1.204 per year; 95% CI 1.084 to 1.336; p<0.001) was significantly associated with severe disability at the last follow-up (table 4).

DISCUSSION

We aimed to identify the effect of earlier rituximab treatment on long-term disability in patients with NMOSD (most of them were previously on immunosuppressants or oral steroids). In a large retrospective study of 145 patients receiving rituximab treatment (mean disease duration of 121 months), we found that earlier initiation of rituximab, together with lower maximal EDSS before rituximab were significantly associated with lower long-term disability. This effect of earlier rituximab treatment was more evident among patients with disease onset at <50 years of age, women, and those with a maximum EDSS≥6 before rituximab treatment. Earlier initiation of rituximab therapy was also significantly associated with a higher chance of ambulation without assistance.

Since Cree *et al* first reported that the use of rituximab significantly reduced post-treatment EDSS compared with pretreatment EDSS in patients with NMOSD,[20] rituximab has been considered an effective treatment regimen for patients with NMOSD. A recent meta-analysis including 29 studies using rituximab reported that EDSS was improved by an average of −0.57 and annualised relapse rate (ARR) was reduced by an average of −1.57.[13] A multicentre, randomised, double-blind, placebo-controlled study demonstrated that rituximab prevented relapses in patients with NMOSD with AQP4 antibody positivity for 72 weeks.[12]

However, rituximab was not initially considered for patients with NMOSD. Recently, eculizumab, satralizumab and inebilizumab were approved by the FDA for the treatment of NMOSD, but rituximab is still used off-label. Rituximab also has some adverse effects, including infection, infusion-related reactions and other serious adverse events,[21] and there is concern that patients taking rituximab may be at an increased risk of infection related to the COVID-19 pandemic. A recent study reported that patients taking rituximab had an increased risk of COVID-19 and serious complications.[22] Therefore, it is not reasonable to use rituximab in all patients. Individualised therapy that selects patients expected to have favourable outcomes and initiates

Table 4 Factors affecting the severe long-term disability (final EDSS≥6) in patients with NMOSD treated with rituximab

	Univariable			Multivariable		
Characteristics	OR	95% CI	P value	OR	95% CI	P value
Gender (male)	1.025	0.264 to 3.990	0.971			
BMI (per kg/m^2)	1.020	0.895 to 1.163	0.761			
Onset age (per year)	0.986	0.952 to 1.020	0.413			
AQP4-Ab positivity antibody	1.074	0.211 to 5.479	0.932			
Maximum EDSS score before rituximab	1.874	1.411 to 2.489	<0.001	1.764	1.004 to 3.099	**0.048**
Concomitant autoimmune disease	0.722	0.249 to 2.091	0.548			
Time to initiation of rituximab (per year)*	1.195	1.099 to 1.298	<0.001	1.204	1.084 to 1.336	**0.001**
Location of first attack	1.147	0.791 to 1.663	0.470			
Maximal length of spinal cord lesion	1.076	0.992 to 1.167	0.079			
Severe ON	1.030	0.429 to 2.476	0.946			
Ambulation without assistance at initiation of rituximab	17.507	4.834 to 63.402	<0.001	4.308	0.428 to 43.37	0.215
Total infusion no of rituximab	0.981	0.851 to 1.131	0.791			
Dose of combined steroid at initiation of rituximab (mg)	0.986	0.963 to 1.010	0.244			
Plasmapheresis before rituximab†	2.818	1.083 to 7.331	0.034			
Rituximab induction‡	0.799	0.394 to 1.621	0.534			
Continued rituximab treatment till last follow- up	0.405	0.122 to 1.338	0.138			
Rituximab maintenance§	1.173	0.510 to 2.697	0.708			

P-value < 0.05 on multivariate analyis appears as bold

*Time to initiation of rituximab: interval from first symptom onset to initiation of rituximab treatment.

†Plasmapheresis before rituximab was not included in the multivariable logistic regression model because of severe multicollinearity between plasmapheresis before rituximab and maximum EDSS score before rituximab and non-significance (OR=1.31 (0.45, 3.81), p=0.623) when adjusted for maximum EDSS score before rituximab (online supplemental table E2).

‡Rituximab induction regimen was classified into three categories: (1) 375 mg/m^2 infused weekly for 4 weeks (reference category), (2) 1000 mg infused twice at 2 weeks interval and (3) other.

§Rituximab maintenance regimen was classified into three categories: (1) fixed time points infusion (reference category), (2) infusion based on CD19 or CD27 counts and (3) other.

AQP4-Ab, aquaporin-4 antibody; BMI, body mass index; EDSS, Expanded Disability Status Scale; NMOSD, neuromyelitis optica spectrum disorder; ON, optic neuritis.

treatment at the proper time for each patient is necessary. However, delayed treatment may cause irreversible neural injury and aggravation of the disability. In our study, deferring rituximab treatment by 1-year increased EDSS by 0.135 points and increased the risk of being unable to walk independently by 1.29 times.

Previous studies have suggested that rituximab is more effective than azathioprine and mycophenolate. Poupart *et al* reported that the risk of relapse was significantly higher in patients treated with mycophenolate mofetil than in those treated with rituximab.[2] In addition, rituximab was more effective than azathioprine in a randomised clinical trial in which both azathioprine and rituximab reduced the ARR and EDSS, but the rituximab group presented more favourable results.[6] In MS, recent studies have reported that high-efficacy treatment at an early stage is an effective way to achieve favourable long-term outcomes[14 15]; however, there are not enough studies about this for NMOSD. Our study demonstrated that earlier treatment with rituximab was associated with a favourable prognosis and prevention of worsening of long-term disability in patients with NMOSD. In addition, the time to initiation of rituximab was a significant determinant factor for EDSS at the last follow-up, especially in patients with early to middle-age onset, women and patients with a maximum EDSS≥6 before rituximab treatment, in our subgroup analysis. This result implies that initiation of rituximab at an early stage is a more effective way to achieve a good prognosis in women with early-age to middle-age onset and severe disability. Age at onset was known as significant factor associated with prognosis in NMOSD. The patients with NMOSD with older age at onset can be associated with poor outcome, due to the less complete recovery from previous attacks and comorbidities in this group.[23] Moreover, though primary astrocytopathy is considered to be a key pathogenesis in NMOSD, demyelination can also be found in patients with NMOSD[24] and experimental models.[25] Recent studies showed that remyelination capacity through a retinoid-X receptor agonist in humans can decrease with ageing, which can support our results of more beneficial effect of early rituximab in younger age group.[26]

A recent study using the National Health Insurance Research Database reported that the prevalence and incidence of NMOSD in Korea have rapidly increased over time.[27] Therefore, early proper intervention before irreversible damage might prevent severe disability in patients with NMOSD and reduce the social burden. Patients with NMOSD sometimes require immunosuppressive agents for a long duration; therefore, consideration of adverse events is necessary. Rituximab has presented few severe adverse effects in many studies, including ours, and is generally well tolerated.

It has been reported that secondary progressive disease course is uncommon in NMOSD,[28] thereby it is quite reasonable to expect that the number of relapse before rituximab can also affect final disability of patients. However, according to our multivariate analysis, time to initiation of rituximab could be more important for better outcome than total number of attacks before rituximab treatment. Several possibilities can be considered for this result. First of all, rituximab has been shown to improve disability as well as reduce relapse rates in patients with NMO.[1] Our study found that early rituximab treatment prevented long-term disability worsening, particularly in patients with severe disability. It is presumed that the early use of rituximab, especially those who experienced of severe attack, can improve degree of disability, and eventually led to a better prognosis. Moreover, slow progression of neurological damage over a long term can be found in patient with NMOSD independently of overt relapses.[29] Together with our data, we speculate that early rituximab use might prevent this slow long-term neurological deterioration in NMOSD. Finally, initiation of rituximab treatment in an earlier disease phase will contribute to maintain a low rate of relapse for the longer proportion of disease courses, which in term can contribute to better disability outcomes.

Recent systemic review has reported high efficacy and safety of rituximab and new medications such as eculizumab, satralizumab and inebilizumab.[30] Among them, rituximab has been shown to have a superior effect compared with classical immunosuppressants such as azathioprine or mycophenolate in previous studies.[6 31–33] Additionally, the annual cost of rituximab treatment in USA can be US$18 000 a year,[34] which is significantly lower than the newer treatment options (The cost of eculizumab is about US$710 000 a year, satralizumab US$219 000 the first year and US$190 000 a year after that, and inebilizumab US$393 000 the first year and US$2 62 000 a year after that,[34 35] so might be more accessible to patients with NMOSD who still experience relapses despite classic immunosuppressant treatment.

This study had some limitations. The rituximab regimen was not the same for each patient and is retrospective design of data. In the subgroup analysis, the effect of earlier rituximab treatment could not be clearly demonstrated in the male group owing to the small sample size.

In conclusion, earlier initiation of rituximab treatment is effective for favourable long-term outcomes in patients with NMOSD, especially for early-age to middle-age onset and in female patients and patients with severe disability. Further studies are needed to clarify effectiveness of rituximab as first-line treatment compared with second-line treatment and to develop predictive biomarkers for the response to rituximab.

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