Rituximab in central nervous system manifestations of patients with primary Sjögren's syndrome: results from the AIR registry

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Abstract

Objectives

To evaluate the efficacy of rituximab in central nervous system (CNS) manifestations of patients with primary Sjögren's syndrome (pSS).

Methods

Prospective data from patients with pSS and CNS involvement included in the French AutoImmunity and Rituximab registry were analysed. All patients had diffuse white matter T2-weigted hypersignals. Neurological response was defined as improvement or disappearance of neurological signs.

Results

Eleven patients (mean age 55 years [38–77]) were treated with rituximab for their neurological involvement. The mean duration of pSS was 9 years (4–24). Mean baseline ESSDAI score was 17 (5–25). Neurological features were progressive multiple sclerosis-like manifestations (n=6), transverse myelitis (n=1), anxiety and depression disorder (n=1) and cognitive dysfunction (n=3). Mean Expanded Disability Status Score (EDSS) before rituximab was 4 (3–5.5). The mean follow-up was of 13 months (6–58). No neurological change occurred in all 6 patients with multiple sclerosis-like symptoms, in 2/3 patients with cognitive dysfunction or in the patient with anxiety-depression. One patient with depression and cognitive dysfunction disclosed subjective improvement. One patient with transverse myelitis, refractory to cyclophosphamide had an improvement of his walk perimeter (160 metres vs. 116). Mean EDSS score and ESSDAI remained stable.

Conclusion

Rituximab does not seem to be effective in progressive multiple sclerosis-like manifestations of patients with pSS-related CNS involvement.

Key words

rituximab, primary Sjögren's syndrome, central nervous system involvement

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Introduction

Primary Sjögren's syndrome (pSS) is an autoimmune systemic disorder affecting mainly the exocrine glands. The hallmarks of pSS involve a dry syndrome associated with asthenia and pain, but systemic complications can occur. Among them, central nervous system involvement (CNS) is one of the most severe complications of the disease. Its frequency remains debated, but the frequency of 20% suggested decades ago (1) is now considered to be around 5% (2). No guideline exists concerning therapeutic management of this complication (2, 3).

B cells play a central role in pSS, acting as autoantigen-presenting cells and producing autoantibodies. Following its evaluation in systemic lupus erythematosus (SLE) and other autoimmune diseases, rituximab (RTX), an anti-CD20 monoclonal antibody, emerged as a possible therapeutic tool in pSS patients (4-7).

No study has assessed the efficacy of RTX in pSS with CNS involvement. Only rare case reports of patients with pSS-related CNS involvement treated with RTX have been reported (8, 9). In SLE-related CNS involvement, open studies suggested the efficacy of RTX. In the largest open study of 10 SLE patients with CNS involvement only 1 had myelopathy and 6 had abnormal signals in the brain white matter (10). Of note, some patients with pSS-related CNS involvement may have neurological impairment and brain diffuse white matter abnormalities on magnetic resonance imaging (MRI) mimicking multiple sclerosis (3).

We evaluated the safety and the efficacy of RTX in patients with pSS-related CNS involvement associated with diffuse brain white matter MRI abnormalities, using the prospective data of the AutoImmunity and Rituximab registry (AIR).

Patients and methods

Patients

Prospective data from all patients with pSS, CNS clinical involvement and brain diffuse white matter abnormalities included in the AIR registry were analysed. AIR is a multicentre registry promoted by the French Society of Rheumatology and the Club Rhumatismes et Inflammation, which includes patients treated with rituximab for refractory autoimmune diseases.

All patients with pSS fulfilled American-European Consensus Group criteria. pSS-related CNS involvement was defined by the presence of central nervous clinical impairment associated with diffuse white matter T2-weigted hypersignal after exclusion of other causes of CNS involvement.

Data for all patients were analysed in the registry electronic CRF, as well as in the patient's chart for patient characteristics, including diabetes and hypertension, disease duration, treatments before RTX, indication, administration regimen and tolerance of RTX. Disease activity was assessed using the European Sjögren's Syndrome Disease Activity Index (ESSDAI) (11).

In all patients, following laboratory data were recorded if available: standard laboratory tests, serum gammaglobulins, CH50%, C3 and C4 levels, rheumatoid factor, protein immunofixation, antinuclear and anti-DNA antibodies, serum cryoglobulin, antiphospholipides antibodies, C-reactive protein, erythrocyte sedimentation rate and % CD19 cells, HIV, TPHA-VDRL, borrelia serologies and cerebrospinal fluid (CSF) analysis.

MRI was abnormal in all 11 patients.

Data were collected at baseline, at the 3- and 6-month follow-up, and then every 6 months.

Neurological response to RTX was defined by the clinician in charge of the patient, as a complete disappearance or improvement of neurological clinical signs. Expanding Disability Status Scale (EDSS) was also assessed for patients with multiple-sclerosis-like symptoms.

This study was approved by the ethics committee. Written informed consent was obtained from all patients.

Statistical analysis

Data are presented as medians with extreme ranges for continuous variables and numbers with percentages for qualitative variables. Fisher's exact test was used to compare qualitative variables and the non-parametric Mann-Whit-

ney U-test for continuous variables. A $p<0.05$ was considered statistically significant. Statistical analyses were realised using GraphPad Prism (GraphPad Software, San Diego, 2007).

Results

Patient's characteristics

Among the 101 patients with pSS included in the AIR registry, 11 patients (11%) had pSS-related CNS involvement with brain diffuse white matter MRI abnormalities and received RTX for their neurological manifestations. The main patient's characteristics are detailed in Table I. Median duration between the onset of CNS involvement and RTX initiation was 87 months (16–251).

Neurological features were multiple sclerosis-like manifestations in 6 patients (54%), with spastic paraparesis and sphincter dysfunction in 3 cases, and focal manifestations in 3 cases (Table II). A transverse myelitis was present in 1 case. Severe anxiety and depression associated with chronic headache and cognitive dysfunction were present in 1 patient. Mild cognitive dysfunction, evidenced by neuropsychological testing, was noted in 3 patients (27%), with particular deficit in the areas of memory, attention and concentration in 2 cases and dysexecutive syndrome in 1 case. Cerebral MRI showed white matter hyperintensities in subcortical and periventricular areas in all cases, but without gadolinium enhancement in all cases. Medullar MRI was abnormal in 4/10 cases, with intramedullar T2-weigted hyperintensities without gadolinium enhancement. Peripheral nervous system involvement was associated in 3 patients (27%), with 2 sensory-motor cryoglobulin-related polyneuropathy and 1 sensory painful neuropathy. One patient had mild treated arterial hypertension.

On top of the neurological involvement, other systemic manifestations were observed in 5 patients, affecting joints (n=4), skin (n=2) and muscle (n=1). Hypergammaglobulinaemia was observed in 4 patients, cryoglobulinaemia in 2, lymphopenia in 3 and anaemia in 1 case. Baseline median ESSDAI was 17 (5–25).

Previous treatments included corticosteroids in 5 patients (45%), with median daily prednisone of 10 mg (5–15). Other immunosuppressant agents had been previously associated in 7 patients (64%): azathioprine and mycophenolate mofetil in 2 patients each (29%); methotrexate, cyclophosphamide and cyclosporine in 1 patient each (14%), but were not modified in 2 months before RTX.

Table I. pSS patient's principal characteristics.

	n=11
Clinical data	
Age (years)	55 [38–77]
Sex (females)	10 (91%)
Disease duration (years)	9 [4–24]
Organ involvement (n; %)	
Skin	2 (18%)
Pulmonary	0
Renal	0
Joint	4 (36%)
Haematological	4 (36%)
ESSDAI before rituximab	17 [5–25]
Laboratory data	
ESR (mm/h)	12 [2–87]
C-reactive protein (mg/L)	2 [0–28]
Gammaglobulins (grammes)	12 [5–20]
Anti-Ro/SSA	7 (65%)
Previous treatments	
Corticosteroids (n; %)	5 (45%)
Corticosteroids dose (mg/day)	10 [5–15]
Immunosuppressant agents (n; %)	7 (64%)
Rituximab regimen	
1g x 2 (n; %)	9 (82%)
375 mg/m^2 x 4 (n; %)	2 (18%)
Rituximab associated treatments	
Corticosteroids (n; %)	7 (64%)
Immunosuppressant agents (total; n; %)	5 (45%)
Cyclophosphamide	3 (27%)
Mycophenolate mofetil	2 (18%)

Values are in medians with ranges and numbers with frequencies.

Rituximab treatment

The type of RTX regimen is indicated in Table I. All patients received 100 mg bolus of corticosteroids before RTX infusion. Corticosteroids were associated with RTX in 7 patients at 10 mg/day (5–60). Other concomitant immunosuppressant agents included cyclophosphamide (n=3, 27%) and mycophenolate mofetil (n= 2, 18%).

Efficacy

Median number of post-RTX visits was 3 (1–5). Median follow-up was 13 months (6–58) from the last RTX infusion.

Table II. Characteristics of the pSS-related neurological involvement.

Patient's characteristics	n=11
Central nervous system involvement	(n, %)
Multiple sclerosis-like	6 (55)
Cognitive dysfunction	3 (27)
Transverse myelitis	1 (9)
Anxiety with depression	1 (9)
EDSS scale before rituximab	4 [3–5.5]
Delay neurological signs-rituximab (months)	87 [16–251]
Associated peripheral nervous system involvement	3 (27)
Associated peripheral nervous system involvement	(n, %)
Sensory-motor polyneuropathy	2 (67)
Sensory painful neuropathy	1 (33)

No neurological improvement was observed in 6 patients with multiple sclerosis-like progressive symptoms, as well as in 2 patients with cognitive dysfunction and in the patient with severe anxiety and depression. The patient with transverse myelitis with recurrent fall experienced improvement in walk perimeter (160 *vs*. 110 metres) at 3 months visit, which remained stable. A significant subjective improvement was also noted in the patient with severe depression and cognitive dysfunction 3 months after RTX. EDSS score, which was 4 (3.5–5.5) at baseline, remained stable at 3, 6 and 9 months: 3.5 (3–5), 3.3 (3–5) and 4 (3–5), respectively (p=0.3). Consecutive cerebral MRI showed no improvement in all 6 evaluated patients at 6 months. CD19 cells were undetectable at 3 and 6 months in 6/6 and in 7/7 patients, respectively.

Median ESSDAI index, which was 17 (5–25) at baseline, remained stable at 3, 6, and 9 months: 15 (7–19), 15 (7–29) and 15 (7–30) respectively (p=0.4). Joint (n=4/4) and skin improvement (n=2/2) was noted in all patients at 3 months.

Two patients were retreated with RTX for a non-neurological indication. A patient was retreated 15 months after the first cycle of RTX because of relapse of her joint involvement, and experienced again an improvement. Another patient with skin, joint and muscular involvement experienced a relapse of these symptoms at 6 months, and was retreated by RTX, but did not experience any improvement.

Table III. pSS patient's neurological features, treatments and outcome.

Patient	Neurological features	Initial EDSS	Initial ESSDAI	Evolution	Treatments before RTX	CS before RTX dose (mg/day)	Associated treatments	Outcome after RTX	Follow-up (months)
1	VII cranial nerve, spastic paraparesis, sphincter dysfunction and cerebellar ataxia	4	17	recurrent then progressive	CYC azathioprine	7	–	stability	8
2	Optic neuritis, cerebellar ataxia, spastic paraparesis, sphincter dysfunction	4	5	recurrent then progressive	–	–	CYC	stability	17
3	Left spastic hemiparesis	4	16	progressive	–	–	–	stability	10
4	Optic neuritis, right spastic hemiparesis	4	23	recurrent then progressive	–	–	–	worsening	13
5	Optic neuritis, right spastic hemiparesis, tetrapyramidal pyramidal signs	5	5	progressive	CYC cyclosporine	–	CYC	worsening	40
6	Anxiety, depression and cognitive dysfunction	3	10	progressive	–	–	CYC	improvement	6
7	Cerebellar ataxia, transverse myelitis	5.5	15	progressive	CYC-MYC	10	MYC	improvement	42
8	Cerebellar ataxia, spastic paraparesis, sphincter dysfunction	4.5	18	recurrent then progressive	CYC-azathioprine	–	–	stability	8
9	Subcortical cognitive dysfunction and cryoglobulin-related polyneuropathy	3.5	25	progressive	MYC	15	MYC	stability	58
10	Headache, severe anxiety with depression and painful sensory neuropathy	2	22	progressive	IgIV-methotrexate	10	–	worsening	11
11	Subcortical cognitive dysfunction with cryoglobulin-related polyneuropathy	6	17	progressive	–	5	–	worsening	15

F: female; M: male; RTX: rituximab; CS: corticosteroids; CYC: cyclophosphamide; MYC: mycophenolate mofetil; IgIV: intravenous immunoglobulins.

Safety

A mild infusion reaction was observed, but did not result in RTX discontinuation. A severe infection (CMV colitis 18 months after RTX) was observed in a patient with acquired hypogammaglobulinemia and concomitant treatment with mycophenolate mofetil.

One patient died in the context of cognitive degradation and weight loss 11 months after RTX perfusion.

Discussion

We analysed the efficacy and the safety of RTX in patients with pSS-related CNS involvement. The safety of RTX was good, but this study did not show clinical efficacy of RTX, in particular in patients with multiple sclerosis-like symptoms. The 2 patients who improved had in one of them transverse myelitis, a CNS complication known to be sensible to immunosuppressive drugs (12) and in the other anxiety with depression and cognitive dysfunction, which is subject to spontaneous fluctuations. Moreover, these 2 patients have associated immunosuppressive drugs, cyclophosphamide and mycophenolate mofetil, respectively, which could cause the improvement. MRI reevaluated 6 months after RTX in 6 patients (including the patient with anxiety and depression) did not improve, but radiological improvement could occur later in patients with progressive CNS course. Stabilisation of the disease in 5 patients could have been considered as an interesting result, but follow-up is low in 4 of these 5 patients and we do not think these cases can argue in favour of the efficacy of RTX. Conversely, efficacy of RTX on extra-neurological involvement was observed, in particular on joint and skin features.

The neurological manifestations of our patients were similar to those previously reported in pSS (3, 13). The lack of classification criteria for CNS involvement in pSS makes it difficult to distinguish it from other neurological diseases, in particular multiple sclerosis. Nevertheless, extraglandular manifestations, present in 56%, and anti-Ro/SSA antibodies, positive in 64%, are infrequent in multiple sclerosis. Other causes of multiple brain white-matter MRI hyperintensities are ageing, hypertension and diabetes. Even though median age was 55 years, no patient presented diabetes and 1 had controlled hypertension.

The heterogeneity of neurological manifestations and the lack of gold standard treatment in pSS result in the absence of therapeutic guidelines. Thus, different immunosuppressant agents, in particular cyclophosphamide, were used in pSS with CNS involvement (14). In spite of long CNS duration before RTX (87 months [16–251]), all patients had progressive disease which justified treatment intensification. The low prevalence of gadolinium-enhancing lesions in patients with pSS is usual and supports the relationship of CNS symptoms with a low inflammatory disease activity (15).

Several studies reported an improvement with RTX in pSS (4-7, 16-19). Improvement of subjective symptoms was noted in several studies, and two studies showed objective glandular improvement (4, 20). An improvement of some extraglandular manifestations was observed, notably joint and cryoglobulin-related symptoms (6, 7, 16). Regarding pSS-related CNS involvement, only 2 patients had a favourable outcome after RTX: a patient with mental nerve neuropathy and abnormal MRI, and a patient with transverse myelitis (8, 9).

Some reasons could be raised to explain the lack of efficacy of RTX on CNS symptoms. In particular, long-standing pSS patients were included in this study, with pSS duration of 9 years and CNS duration of 7 years. More than half of patients were refractory to other

immunosuppressant agents. Damage rather than disease activity might have been responsible for the neurological impairment, as reflected by the absence of gadolinium-enhanced lesions and the low level of systemic activity according to the ESSDAI. Of note, in 104 patients with relapsing remitting multiple sclerosis, the primary endpoint was the reduction of total count of gadolinium-enhancing lesions (21). Interestingly, in the second controlled trial involving 439 patients with multiple sclerosis, no significant efficacy was observed regarding the primary endpoint (time to disease progression), but a subgroup analysis showed a possible efficacy in younger patients and in those with gadolinium-enhancing lesions (22).

Conclusion

RTX does not seem to be effective in pSS with multiple sclerosis-like symptoms. Additional studies are needed to confirm these data, in particular in early-onset disease and to assess the RTX efficacy in other pSS-related neurological manifestations.

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Author's contributions

A. Mekinian, J.-E. Gottenberg and X. Mariette were involved in the data analysis and wrote and edited the manuscript. P. Ravaud, C. Larroche, E. Hachulla, B. Gombert, C. Blanchard-Delaunay, A. Cantagrel, O. Fain and J. Sibilia assisted with the editing of the manuscript, the subject matter content and the conclusion. All authors were involved in the discussion of the findings as well as the drafting of the manuscript.

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