Rituximab Treatment for Spondyloarthritis. A Nationwide Series: Data from the AIR Registry of the French Society of Rheumatology

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ABSTRACT. ***Objective.*** To evaluate the efficacy and safety of rituximab (RTX) in several subsets of spondyloarthritis (SpA) using the data of the AIR (Autoimmunity and Rituximab) registry.

Methods. All patients receiving RTX for SpA, and prospectively included in the AIR registry from September 2005 to September 2010, were retrospectively analyzed. The response to treatment was evaluated by the Bath Ankylosing Spondylitis Disease Activity Index for axial disease, joint count for peripheral disease, and C-reactive protein reduction.

Results. Among the 595 patients included in the AIR registry, 26 patients with SpA from 13 centers were reported: ankylosing spondylitis (10), undifferentiated SpA (7), and psoriatic arthritis (9). Mean disease duration was 8.8 years (range 1–40). The extraarticular features found were psoriasis, 12 cases; uveitis, 4 cases; and Crohn's disease, 3 cases. The mean number of disease-modifying antirheumatic drugs before RTX was 2.4; previous anti-tumor necrosis factor (TNF) agents were taken in 23 cases. The mean number of RTX courses was 1.5 (range 1–5), with a total of 35.6 patient-years. Efficacy was noted in 11/23 cases: 3 out of 3 anti-TNF-naive patients and 8 out of 20 anti-TNF nonresponder patients. No predictive factors of response could be identified, particularly in diagnosis subsets or clinical presentation (axial or peripheral).

Conclusion. In this nationwide study of several subsets of SpA, RTX had only a moderate efficacy that was more marked in patients who were anti-TNF-naive. (J Rheumatol First Release Aug 15 2012; doi:10.3899/jrheum.120201)

Key Indexing Terms:
RITUXIMAB SPONDYLOARTHRITIS PSORIATIC ARTHRITIS
ANKYLOSING SPONDYLITIS AIR REGISTRY

The concept of spondyloarthritis (SpA) encompasses several entities such as ankylosing spondylitis (AS), reactive arthritis, psoriatic arthritis (PsA), inflammatory bowel disease (IBD)-associated arthritis, and undifferentiated SpA. B lymphocytes may be implicated in the immune modifications associated with the disease[1,2]. Elevated immunoglobulin A (IgA) levels have been demonstrated in AS and correlated with disease activity[3]. In addition, B lymphocyte infiltrates were found in zygapophyseal joints of patients with AS, in association with inflammatory magnetic resonance imaging (MRI) lesions[4].

Rituximab (RTX) is a monoclonal chimeric antibody directed against CD20 and targeting the B lymphocyte. Data about RTX use in SpA are scant, with few case

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The AIR registry was supported by an unrestricted grant from Roche France.

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Accepted for publication June 21, 2012.

reports[5,6,7,8] and small series[9], one prospective open study[10], and no controlled studies. Thus, observational results from a prospective registry might be of interest to increase knowledge of RTX efficacy in SpA.

Our aim was therefore to evaluate the efficacy and safety of RTX treatment in patients with several subsets of SpA, using the data of the AIR (Autoimmunity and Rituximab) registry.

MATERIALS AND METHODS

The AIR registry is an ongoing nationwide prospective cohort study that since September 2005 has collected data on patients with autoimmune diseases (systemic lupus erythematosus, myositis, vasculitis, primary Sjögren's syndrome, and other inflammatory arthritides). The AIR registry was set up by the French Society of Rheumatology and its section the Club Rhumatismes et Inflammation to investigate the longterm safety and efficacy of RTX for treating these disorders. All French hospital-based and community-based units (rheumatology, internal medicine, dermatology, and pediatrics) were invited to take part in this observational registry. The registry includes data from 82 centers.

Data concerning patient characteristics, indications, therapy regimen, and tolerance and efficacy of RTX were prospectively collected at baseline and at the 3-month and 6-month followup, then every 6 months or at disease relapse, by use of an electronic case report form.

All patients receiving RTX for SpA, and included in the AIR registry from September 2005 to September 2010, were eligible for the study and retrospectively analyzed. Diagnosis of SpA was based upon modified New York criteria for AS, Amor criteria for undifferentiated SpA, and Vasey and Espinoza criteria for PsA.

Our study was approved by the appropriate ethics committee. Informed consent was obtained from all patients. Treatment regimen was 1 g RTX given intravenously, twice at 2-week intervals, after premedication. The patients may have had several courses of treatment.

Efficacy. The initial response to treatment was evaluated at 3 months and 6 ± 1 month after treatment, according to the main clinical presentation/ subset of the disease, by reduction of the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) over 2 units (on a 0–10 scale) for axial disease, swollen joint count reduction over 20% for peripheral disease, and a C-reactive protein (CRP) reduction of at least 20% in patients with elevated CRP levels at baseline. Composite indexes such as the Assessment of Spondyloarthritis International Society (ASAS20) response or Ankylosing Spondylitis Disease Activity Score variation could not be retrospectively calculated.

Statistical analysis used the Wilcoxon test for continuous variables; p values < 0.05 were considered significant.

Adverse events. Adverse events were recorded, such as infusion reactions, extraarticular features (uveitis, skin disease, IBD), serious infections (defined as an infection requiring hospitalization and/or intravenous antibiotics), surgical complications, and death or occurrence of cancer.

RESULTS

Among the 595 patients included in the AIR registry in September 2010, 26 with SpA, from 13 centers, had been treated with RTX (Tables 1 and 2). The mean age was 51 years (range 20–76); 13 were men. The diseases were AS (10 cases), undifferentiated SpA (7 cases), and PsA (9 cases). The clinical presentation was exclusively axial in 8 cases, exclusively peripheral in 8 cases, and axial and peripheral in 10 cases. The mean disease duration was 8.8 years (range 1–40), with some extraarticular features, as follows: currently having or history of psoriasis, 12 cases; uveitis, 4 cases; and Crohn's disease, 3 cases. The mean number of disease-modifying antirheumatic drugs used before RTX was 2.4, and a previous tumor necrosis factor (TNF) blocker was used in 23 cases (mean 2.3). Three cases did not receive previous TNF blockers because of contraindications. Nineteen patients received only 1 cycle of RTX, and for the whole population (26 patients) the mean was 1.5 (range 1 to 5) courses, with an interval of 6–18 months between treatment courses. The mean followup was 17.8 months, with a total of 35.6 patient-years.

Efficacy could be assessed in 23 cases. A response to RTX was observed in 11 patients (47.8%); this occurred between 3 and 7 months after treatment (Table 3). In responders, mean BASDAI decreased from 62 to 28 mm ($p < 0.005$) in the 7 patients with axial symptoms (but only 3 patients reached a BASDAI 50 level of response). Mean swollen joint count declined from 4 to 1 ($p < 0.05$) in predominantly peripheral forms (4 cases: 2 PsA and 2 peripheral SpA). Among the 11 responders, mean CRP levels decreased from 45 to 18 mg/l ($p < 0.005$).

Efficacy on extraarticular manifestations was demonstrated by improvement of psoriasis (over 50% reduction of area) in 2 cases (without improvement of the rheumatologic symptoms).

Clinical response was observed in 3 out of 3 anti-TNF-naive patients and 8 out of 20 anti-TNF nonresponder patients. Extraarticular manifestations were as frequent in responders as in nonresponder patients. There were no differences between responders and nonresponding patients in sex, mean disease duration, baseline CRP levels (41.7 mg/l for responders vs 47.4 mg/l in nonresponders), total white blood cell count, and total Ig levels at baseline. Serum baseline IgA levels were higher (although not significantly) in responders compared to nonresponders (3.66 vs 2.46 g/l; $p = 0.4$).

Safety. Treatment was generally well tolerated. One severe infection was recorded after 7 and 16 months (3 serious infections/100 patient-yrs), as well as 1 cardiac failure episode after 7 months. Two moderate infusion reactions out of 80 infusions were noted. No deaths and no cancer occurred.

A worsening of extraarticular manifestations occurred in 4 patients: deterioration of psoriasis in 2 cases; 1 case of uveitis relapse; and 1 case of new onset of uveitis; no deterioration of the underlying IBD was noted. Surgical procedures were performed in 7 cases, 3 to 36 months after RTX, with 2 complications: infection of knee prosthesis (7 mo after RTX), and a case of vein thrombosis after shoulder replacement (5 mo after RTX).

Re-treatments. RTX was discontinued in 12/23 evaluable patients (11 for inefficacy and 1 for adverse events). The mean duration of efficacy was 6.1 months (range 3–12). Seven patients were re-treated (2 to 5 cycles), with an interval ranging from 6 to 18 months between cycles.

Table 1. Patient characteristics.

Patient	Age/ sex	SpA Type	HLA-B27	Disease Duration, yrs	Previous DMARD	Previous Biologic	Associated DMARD	Steroids, mg/day	Extraarticular Features	Associated Diseases
1	46 M	PsA periph		20	AZA, LEF, MTX, gold	ETA, IFX, ADA	0	10	0	0
2	37 F	AS	+	8	SSZ	ETA, IFX, ADA	0	0	0	0
3	49 M	SpA periph		16	MTX, SSZ, LEF, gold	ETA, IFX	0	10	0	0
4	31 F	SpA axial, periph		8	MTX, SSZ, AZA	ETA, IFX ADA	MTX	0	Crohn PSO	0
5	61 F	PsA axial, periph		13	MTX, SSZ, gold	ETA, ADA	MTX	20	PSO	0
6	38 M	AS + oligo	_	15	MTX, SSZ, CTX	ETA, IFX	0	7	Uveitis	0
7	64 F	PsA periph		10	MTX, SSZ LEF, gold	IFX	MTX	40	PSO	0
8	62 M	AS axial	+	40	MTX, SSZ	0	0	0	0	MGUS bladder cancer, HTA
9	56 F	PsA periph, axial		25	MTX, SSZ LEF, gold	ETA, IFX, ADA	MTX	0	PSO	0
10	34 F	AS axial	+	12	MTX, HCQ	ETA, IFX	MTX	50	Uveitis	0
11	65 M	AS axial, periph	+	3	SSZ	ETA, ADA	0	0	PSO Uveitis	Diabetes, coronaropathy
12	69 F	PsA periph		6	MTX, LEF HCQ, CYC	0	0	0	PSO	MGUS, TB history
13	69 M	SpA PSO		NA	MTX, SSZ, LEF	ETA, IFX ADA	LEF	0	PSO	MGUS, prostate cancer, coronaropathy
14	35 F	PsA periph		NA	MTX, LEF	ETA, IFX ADA	0	5	PSO	0
15	56 M	PsA periph		6	MTX, SSZ	ETA, IFX ADA	0	15	PSO	0
16	60 M	AS axial, periph	+	7	MTX	ETA, IFX ADA	SSZ	0	0	HTA
17	20 F	PsA periph		2	MTX, LEF, HCQ	ETA	0	0		
18	65 F	SpA periph	+	4	MTX	ETA, ADA	LEF	0	Uveitis, Crohn	Diabetes
19	56 M	AS axial	+	16	MTX	ETA, IFX ADA	MTX	0	0	0
20	36 M	AS axial, periph		18	MTX, SSZ	ETA, IFX ADA	0	0	0	Still's disease history
21	39 M	SpA	+	18	SSZ	ETA	0	0	0	Chondrosarcoma history
22	61 F	PsA periph, axial		13	MTX, SSZ, gold	ETA, ADA	MTX	15	PSO	
23	55 M	PsA periph, axial		7	MTX, SSZ	ADA, ABA	MTX	0	PSO	MS
24	76 M	SpA axial, periph		9	MTX, AZA	IFX	MTX	5	Crohn	Diabetes, digestive cancer
25	55 F	AS axial	+	21	0	0	0	0	PSO	0
26	41 F	AS axial, periph	+	16	SSZ	ETA, IFX, ADA	0	0	0	Vasculitis

PsA: psoriatic arthritis; periph: predominantly peripheral involvement; AS: ankylosing spondylitis; SpA: spondyloarthritis; AZA: azathioprine; MTX: methotrexate; LEF: leflunomide; SSZ: sulfasalazine; HCQ: hydroxychloroquine; CTX: cyclophosphamide; CYC: cyclosporine; gold: gold salts (allochrysine); ETA: etanercept; ADA: adalimumab; IFX: infliximab; ABA: abatacept; PSO: psoriasis; MGUS: monoclonal gammopathy of undetermined significance; HTA: arterial hypertension; TB: tuberculosis; Crohn: Crohn's disease; MS: multiple sclerosis.

Table 2. Summary of case results.

Patient	No. RTX Cycles	Adverse Events	Clinical Efficacy/ Response	Duration of Followup Available, mo	Comments
1	1	0	No	18	
2	1	0	No	6	
3	3	Uveitis	Yes	24	
4	2	Fever, PSO recurrence	No	24	
5	1	0	No	24	
6	1	Relapse of uveitis	No	6	Lost to followup
7	1	0	Yes	14	
8	5	0	Yes	48	
9	1	Rash	No	18	
10	2	0	Yes	12	
11	1	0	Yes	4	Lost to followup
12	1	Severe infection	Yes	18	Knee prosthesis infection after 7 mo, septicemia after 16 mo
13	5	Cardiac failure	No	40	PSO improvement by 50%
14	1	0	Not evaluable	6	
15	1	0	No	18	
16	1	0	Not evaluable	NA	Lost to followup
17	1	0	Not evaluable	NA	Lost to followup
18	1	0	Yes	12	
19	1	0	No	30	
20	1	Mediastinal adenomegaly after 2 yrs	Yes	24	
21	1	0	No	18	
22	1	0	No	9	
23	2	PSO exacerbation	Yes	26	
24	1	0	Yes	4	
25	2	0	Yes	10	
26	1	0	No	24	

RTX: rituximab; PSO: psoriasis; NA: not available.

Table 3. No. patients included/responding, according to the diagnosis and classification of spondyloarthritis, and to the clinical rheumatologic presentation.

Distribution/Responders			
Diagnosis	PSA 9/3	AS 10/5	SpA 7/3
Clinical presentation	Peripheral 8/4	Axial 8/3	Axial and peripheral 10/4

PsA: psoriatic arthritis; AS ankylosing spondylitis; SpA: undifferentiated spondyloarthritis.

DISCUSSION

We report the nationwide real-life experience of RTX treatment of patients with SpA, based on the data of the AIR registry. Despite the limitations of our study (mainly its observational design and the weakness of the criteria for response), it confirms the results reported for the 8 first patients included in the AIR registry[6,9]. Our study allows a view of RTX efficacy in several subsets of SpA. Data from the literature are scant. There are available only a few case reports[5,7,8], 1 prospective open study[10] including 20 patients with AS (10 TNF-blocker-naive and 10 anti-TNF inadequate responders), and 1 open study of 21 patients with peripheral PsA[11]. From these 44 patients (22 AS, 22 PsA), 18 exhibited not only response to RTX treatment on axial symptoms, but also peripheral arthritis[11] or enthesitis, or sacroiliac MRI[8]. The rate of responders in our series is the same (11/23), the response occurring over 3 months after RTX and lasting sometimes for 12 months. Some patients were repeatedly treated (2 to 5 times).

No predictive factors of response could be identified: no difference was observed between responders and non-responders for baseline CRP, presence of HLA-B27, extra-articular features, serum levels of Ig, clinical presentation (axial/peripheral), or classification subsets (AS, PsA, or undifferentiated SpA). However, efficacy seemed better in patients naive for biologic therapy, as shown by Song, *et al*[10] and Mease, *et al*[11] in AS and PsA, respectively.

The safety profile was fair, with only 1 severe infection in these patients (about 3/100 patient-yrs), and with many comorbidities. The effect of RTX treatment on extraarticular features of SpA is balanced, with some cases of improvement and some cases of deterioration of psoriasis; the latter was

previously reported[12,13]. RTX may be beneficial for treating severe uveitis[14], but relapse or new onset of uveitis (1 case each) occurred in our series under RTX treatment; this paradoxical effect is well described with TNF blockers[15].

Despite the improvement observed in some patients, these results do not indicate a major therapeutic effect of RTX in SpA, especially in cases with inadequate response to TNF blockers. Together with the data in the literature, this may suggest that B lymphocyte may not be an adequate candidate for targeted therapy in SpA. Moreover, AS may develop in the absence of B cells[16].

This situation emphasizes the need to optimize anti-TNF therapy on the one hand[17], and the need to evaluate new biologics in cases of anti-TNF failure on the other[18].

ACKNOWLEDGMENT

The authors acknowledge Xavier Mariette (coordinator of the AIR registry), Philippe Ravaud (methodologist of the AIR registry), Isabelle Pane (bioinformatician), and all the investigators of the AIR registry.

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