Clinical and ultrasonographic evaluation of the window of opportunity for retreatment with rituximab in rheumatoid arthritis patients from a multicentre real-life study

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Abstract

Objective

To determine a potential window of opportunity for retreatment with rituximab in patients with rheumatoid arthritis (RA) from a multicentre longitudinal real-life study based on tight monitoring with ultrasonography (US).

Methods

Thirty RA patients treated with rituximab were included. US parameters were collected at each time (8 visits) of the 18-month follow-up, notably the global score of power Doppler (PD) activity. Clinical relapse was defined as a DAS28 ESR of >3.2 after 6 months in responders while US relapse was defined as an increase of ≥20% of the global score of PD activity. The decision of retreatment was based exclusively on clinical findings.

Results

A total of 29 patients were analysed (mean (SD) age: 57.2 (12.2) years; female gender: 66%). The mean (SD) PD score decreased from 8.8 (5.2) at baseline to 4.9 (4.3) at 6 months (p <0.0001). A clinical response was observed at Month 4 or Month 6 for 93% of patients. A total of 19 patients had a first clinical relapse (with or without US relapse) after Month 6 (18 of them were retreated with rituximab). Among 10 patients without clinical relapse, 3 had US relapse (only one was retreated) and 7 had no US relapse (but 4 were retreated).

Conclusion

This study highlights a great heterogeneity in terms of sequence of clinical relapse, US relapse and retreatment in RA patients receiving rituximab. Therefore, US monitoring does not seem to be relevant to determine the best time for retreatment with rituximab.

Key words

rheumatoid arthritis, rituximab, ultrasonography, relapse

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Introduction

The assessment of the efficacy of rituximab in rheumatoid arthritis (RA) includes physical examination and inflammatory markers. Most often, a response to treatment is observed 16 weeks after the first infusion (1). According to international recommendations, a new infusion of rituximab is possible only after 24 weeks if there is a relapse of RA (Disease Activity Score (DAS) >3.2) or after a change of DAS28 >0.6 (2). If there is no response after a first treatment, there is no indication for retreatment. Currently the time of retreatment is decided after a clinical relapse which occurs generally 6–18 months after the first infusion of the first treatment cycle (3). However, these conditions are not satisfactory since a clinical relapse is often detected too late, because of long delays between the reappearance of symptoms and the rheumatology appointment, and a subsequent need to reintroduce long-term corticosteroid therapy while waiting for the next rituximab infusion.

Power Doppler (PD) and grey-scale (GS) ultrasound (US) assessment is a non-invasive imaging method to assess the degree of synovial activity in RA and it could be of interest for deciding the time of retreatment with rituximab. Some authors showed that this method was more sensitive to detect inflammatory processes in joints with a better correlation with inflammatory biological markers compared to clinical examination (4, 5). It has been suggested that joint US for the detection of infra-clinical but active synovitis could be predictive of future osteo-cartilaginous lesions (6). However, only two studies have reported either the US changes of patients treated with rituximab or the possibility to detect disease relapse before clinical symptoms reappear (7, 8). Moreover, evidence-based data for retreatment after US relapse are lacking. The objective of this study was to evaluate in current clinical practice the interest of tight US monitoring for the follow-up of RA patients treated with rituximab and to study the window of opportunity for retreatment.

Materials and methods

Study design

The SEWORRA (Sonography Evaluation of the Window of Opportunity with Rituximab in Rheumatoid Arthritis) study was an open-label, multicentre, regional, longitudinal clinical trial performed in four French centres.

The recommended dose of rituximab is 1000 mg by intravenous infusion followed by a second 1000 mg intravenous infusion two weeks later. Premedication with methyl-prednisolone, levocetirizin-dihydrochloride and acetaminophen was given before rituximab infusion. Rituximab was administered at the inclusion visit (Visit 1; Day 1) and at Day 15 (Visit 2); eight follow-up visits were planned after Day 15 (every two months from month 4 to month 18; Visits 3 to 10). Retreatment was possible during follow-up, according to the decision of the clinical investigator which was based exclusively on clinical findings.

Patients

Patients were eligible if they met the following criteria: ≥18 years of age; RA with inadequate response or intolerance to DMARDs including at least one anti-TNF; DAS28 ESR >3.2. Patients who had previously received rituximab, who had a known contraindication to rituximab or who had participated in another clinical trial (within one month for soluble receptor and within two months for monoclonal antibodies) were excluded. Women of childbearing age not using a medical contraceptive regimen, pregnant women and breastfeeding women were excluded.

Assessments

- Clinical and biological evaluation of rheumatoid arthritis

At the inclusion visit, demographics, disease history, previous and on-going treatments were recorded. At each visit, clinical data: number of tender joints (for a total number of 28), number of swollen joints (for a total of 28), disease activity assessed by the patient with a 100-mm visual analogue scale (VAS), evaluation of synovial volume and tenosynovitis; and biological data: erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were recorded.

DAS28-ESR was calculated to estimate the degree of activity of RA. Physicians were blind to US findings.

- Grey-scale and power Doppler ultrasonographic assessment

In all four centres, the US examination was carried out at the 8 time points by an investigator who had no knowledge of the clinical and biological data of the patient. All centres were equipped with the same apparatus (MyLab 70 (Technos Esaote)) and all assessors had a long-standing experience in US evaluation of RA. They had already participated in several multicentre studies such as that conducted by D'Agostino *et al*. (9). Multiplanar GS and PD assessment was performed with both high-resolution (14–18 MHz) linear transducers and Doppler settings optimised for slow flows (range of pulse repetition frequency: 500–750 Hz; Doppler frequency: 8–10 Mhz). Twelve joints were systematically assessed including wrists, metacarpophalangeal (MCP) joints 2, 3 and 5, proximal interphalangeal (PIP) joints 2 and 3 (10). Synovial changes were evaluated using a semi-quantitative scoring system with a 0–3 scale for GS and PD according to the method developed by Szkudlarek *et al*. (11). Tenosynovial changes observed either in the 6 extensor compartments of the wrist or in the sheaths of the flexor tendons of the fingers complemented the ultrasound examination (10).

Three scores were taken into account, *i.e*. the GS synovial hyperplasia score, the PD synovitis score and a composite score. This latter is the Outcome Measures in Rheumatology-European League against Rheumatism (OMERACT-EULAR) composite PDUS synovitis score which combines intrasynovial PD signal and GS-assessed synovial hyperplasia for evaluating synovial activity (9). For each joint, the OMERACT-EULAR PDUS synovitis score was assessed (Grade 0–3) as a composite of GS (hypoechoic) synovial hyperplasia (Grade 0–3) and PD signal (Grade 0–3) as follows: grade 0 (normal) joint: no GS-detected synovial hyperplasia and no PD signal; grade 1 (mild synovitis): grade 1 synovial hyperplasia and ≤ grade 1 PD signal; grade 2 (moderate synovitis): grade 2 synovial hyperplasia and ≤ grade 2 PD signal or grade 1 synovial hyperplasia and grade 2 PD signal; grade 3 (severe synovitis): grade 3 synovial hyperplasia and ≤ grade 3 PD signal or grade 1 or 2 synovial hyperplasia and grade 3 PD signal. The global score of composite PDUS synovitis of each patient (from 0 to 36) is the sum of the composite PDUS scores of all assessed joints.

US response was defined as a decrease from baseline of >50% of the global score of composite PDUS synovitis and/or a decrease from baseline of >50% of the global score of PD for joints; a decrease from baseline of >50% of the number of tenosynovitis responses and disappearance of the signal of PD for tendons. For patients with a US response, relapse was defined as: an increase of ≥20% of the global score of composite PDUS synovitis and/or an increase of ≥20% of the global score of PD for joints; an increase of ≥20% of the number of tenosynovitis responses and/or reappearance of the power Doppler signal for tendons. Relapse was defined relative to the maximum improvement observed during the visits.

The time of retreatment with rituximab was decided by the clinical investigator and was based exclusively on clinical findings, independently of US findings that were provided by an independent investigator. All investigators scrupulously respected this rule. US data were only analysed after the study was completed.

Sample size calculation

The sample size was determined by estimating the mean of the PD score at six months (primary outcome). In order to have a 95% confidence interval width of less than ± 0.4 times the estimated PD score (standard deviation) at six months and based on Student's t-distribution for the mean PD score, 27 patients had to be included and assessed. In order to reach this target sample size, it was planned to include 30 patients allowing for up to 10% of rituximab retreatment failure (either for lack of efficacy of the first course of rituximab or occurrence of serious adverse effects) or potential loss to follow-up.

Statistical analysis

The primary endpoint was the global score of PD activity measured by ultrasonography on the 12 joints at each time of follow-up. Secondary endpoints were the global score of grey-scale-assessed synovial hyperplasia on the 12 joints evaluated and the global score of composite PDUS synovitis, as previously defined, DAS28, ESR and CRP at each time of follow-up. Clinical response was defined as a DAS28 of ≤3.2. For patients with a clinical response at 6 months, a clinical relapse was defined as a DAS28 of >3.2 after 6 months.

Definitions of US response and relapse have been mentioned in the "assessments" section. Since some data were missing concerning the number of tenosynovitis responses over time, it was not possible to determine whether the tenosynovitis response occurred before or after the articular response (PD synovitis score).

The window of opportunity for retreatment was defined as the time interval between US-evidenced relapse and clinical relapse.

Patients' characteristics are described overall and by groups: clinical responders (including both moderate and good responders) and non-responders at 6 months using standard parameters: mean and standard deviation values for quantitative variables and frequencies and percentages for qualitative variables. Baseline characteristics of clinical responders and non-responders at 6 months were compared using the Pearson's Chi-square test or the Fisher exact test (if necessary) for categorical variables and using the Mann-Whitney test for quantitative variables. The Wilcoxon test was used for comparisons of endpoints at each visit with the baseline visit (the Bonferroni correction for multiple comparisons was applied).

Cohen's kappa was calculated to assess the agreement between clinical response and US response.

To study the relationship between clinical response and US response, the correlation between changes of DAS28 or each of its items and those of the 3 US scores during the first 6 months of follow-up was assessed using Spearman's rank correlation coefficient (point esti-

mate and confidence interval and compared to the null value in order to assess correlation).

Statistical significance was defined as $p<0.05$ (except for the Wilcoxon test). Analyses were performed using SAS software v. 9.3 (SAS Institute; Cary, North Carolina, USA).

Ethics

The study was conducted in accordance with the Declaration of Helsinki and was approved by a local independent Ethics Committee ("Comité de Protection des Personnes Nord-Ouest I"). Written informed consent was obtained from each patient. This trial is registered with ClinicalTrials.gov, no. NCT01765374.

Results

Patients and baseline characteristics

A total of 30 patients were included in the study. There was an early discontinuation at Visit 1 for one patient due to a serious adverse event. In the absence of a second injection of rituximab at Day 15, this patient was not analysed. Among the 29 analysed patients, 20 completed the study at 18 months.

The patients had a mean (SD) age of 57.2 (12.2) years and the majority were female (66%) with long disease duration (12.4 (10.6)) years on average) and high disease activity as assessed by 100 mm VAS, DAS28 and the number of tender and swollen joints. There was no statistical difference between responders and non-responders to rituximab concerning baseline demographic, clinical, biological, ultrasonographic, and therapeutic characteristics at inclusion (Table I)

Table I. Baseline demographic, clinical, biological and therapeutic characteristics of the population studied including 6 clinical non-responders and 23 clinical responders to rituximab at 6 months.

Characteristics	Total population (n=29)	Non-responders (n=6)	Responders (n 23)
Age (years)	57.2 (12.2)	65.3 (11.6)	55.9 (11.4)
Female gender, n (%)	19/29 (66)	4/6 (66.7)	14/22 (63.6)
Disease duration (years)	9.7 (0;36.6)	17.6 (2.5;28.2)	10.0 (0;36.6)
Rheumatoid factors positivity, n (%)	16/28 (57.1)	6/6 (100)	10/22 (45.4)
Anti-CCP positivity, n (%)	25/27 (92.6)	5/5 (100)	20/22 (90.9)
Erosive disease, n (%)	25/29 (86.2)	6/6 (100)	19/23 (82.6)
Previous treatments with bDMARDs, n (%)			
Anti-TNF	24/29 82.8)	6/6 (100)	18/23 (75)
Abatacept	6/29 (20.7)	1/6 (16.7)	5/23 (21.7)
Anakinra	1/29 (3.4)	1/6 (16.7)	0 (0)
Other treaments at inclusion, n (%)			
Methotrexate	14/29 (48.3)	3/6 (50)	11/23 (47.8)
Other DMARD	9/29 (31.0)	2/6 (33.3)	7/23 (30.4)
Prednisone	19/29 (65.5)	5/6 (83.3)	14/23 (60.8)
NSAID	7/29 (24.1)	2/6 (33.3)	5/23 (21.7)
Number of painful joints (out of 28)	10.2 (8.0)	7.0 (5.5)	11.0 (8.6)
Number of swollen joints (out of 28)	8.5 (4.0)	7.3 (3.5)	8.5 (4.1)
Number of tenosynovitis (hand, wrist), n (%)			
0	15 (51.7)	2 (33.3)	13 (56.5)
1	5 (17.2)	1 (16.7)	4 (17.3)
≥2	9 (31)	3 (50)	6 (26)
Disease activity [a] (100 mm-VAS)	62.2 (19.0)	54.2 (11.1)	63.4 (20.2)
DAS28-ESR	5.8 (1.4)	5.5 (1.3)	5.8 (1.4)
DAS28-CRP*	5.2 (1.3)	4.8 (1.2)	5.3 (1.3)
ESR (mm/1sth)	46.1 (37.3)	65.8 (56.8)	41.6 (30.6)
CRP (mg/L)*	26.1 (26.3)	37.5 (29.0)	23.5 (25.8)
Score of grey-scale-assessed synovial hyperplasia*	17.3 (7.8)	14.3 (9.3)	17.7 (7.3)
Score of intrasynovial power Doppler signal*	8.76 (5.23)	10.17 (6.46)	7.95 (4.61)
Composite PDUS synovitis score*	17.6 (7.7)	15.0 (9.3)	17.8 (7.2)

[a]Evaluated by the patient; *CRP and US data were not available for 1 patient at Month 6.
Results are expressed as mean ± SD unless indicated otherwise.

Clinical response

The rate of responders was 72.4% at Month 4 and 75.0% at Month 18. A total of 23 patients (79.3%) were clinical responders at Month 6 (Table II). DAS28 decreased significantly during follow-up compared to baseline (Fig. 1). The mean numbers of tender and swollen joints decreased significantly from 10.2 (8.0) to 2.5 (3.5) and from 8.5 (4.0) to 2.7 (3.0) between baseline and Month 18, respectively. The mean concentrations of C-reactive protein decreased from 26.1 (26.3) to 10.2 (18.5) mg/l (data not shown).

Ultrasonographic measurements

The mean changes of the 3 ultrasonographic scores from baseline to Month 6 according to the degree of clinical response are shown in Table IV. The decrease of the composite PDUS synovitis score and its two components was statistically significant from Month 4 to Month 18 for the overall population (Fig. 1).

At Month 6, concordance between clinical response and US response was moderate with PD only (kappa CI 95%: 0.43 (0.15–0.70) but concordance was low when the composite PDUS score was used (kappa CI 95%: 0.17 (-0.07–0.42). Moreover, concordance between the two components of the composite PDUS score (synovial hyperplasia and PD) was moderate (kappa CI 95%: 0.50 (0.19–0.81).

While there was no correlation between the number of tender joints, global disease activity evaluated by the patient or CRP levels and the 3 US scores, a significant correlation was highlighted between the number of swollen joints and the 3 US scores at the different time points from month 4 to month 18 (data not shown).

In the same way, a correlation was observed between the changes in the number of swollen joints and US score during the first 6 months of follow-up (Table III).

Delays for clinical response and ultrasonographic response

For the 23 clinical responders at Month 6, the mean (SD) delay to clinical response was 139 (33) days. For US responders, the mean delay was 160 (17)

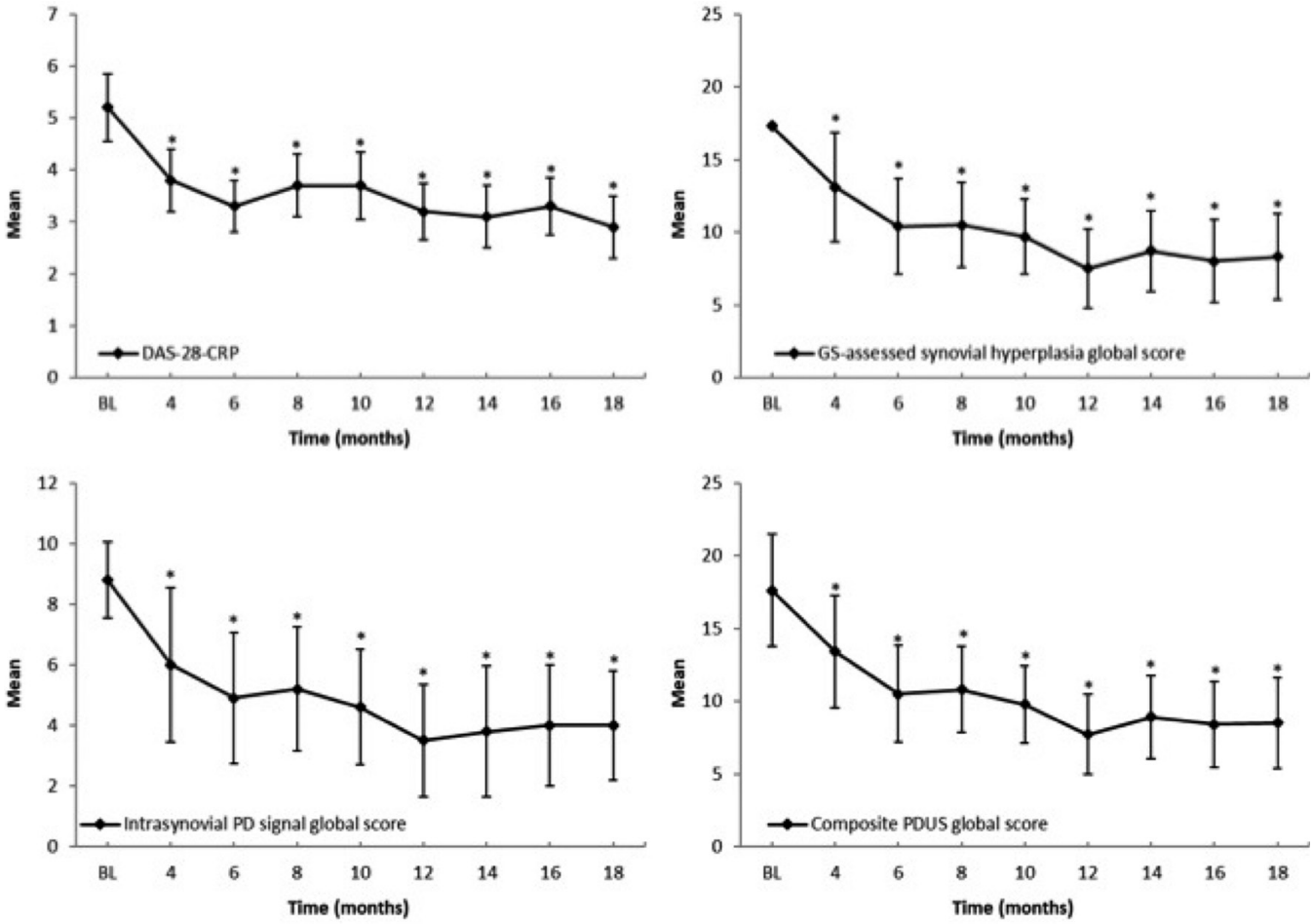

Fig. 1. DAS-28-CRP and ultrasonographic scores at each visit over the 18-months follow-up period. Results are expressed as mean ± SD. *significant differences in comparison with baseline (Wilcoxon test) after using Bonferroni correction (p<0.01666, *i.e.* 0.05/8).

days for the PD synovitis score (n=20) and 197 (80) days for the composite PDUS synovitis score (n=18).

In the 19 patients with both a clinical response and a US response, the latter was recorded later than the clinical response: the mean difference was 22 (56) days on average for the PD synovitis score and 65 (80) days for the composite PDUS synovitis score.

Delays for clinical relapse and ultrasonographic relapse - window of opportunity for retreatment

During follow-up, 7 patients had no relapse, either clinical or evidenced by ultrasonography, and 22 patients had a first clinical relapse and/or a US relapse. For the 19 patients with a first clinical relapse, it was observed after 255 (82) days on average. In patients with a US relapse, it was observed after a mean of 268 (65) days for the PD synovitis score (n=15) and 279 (70) days for the composite PDUS synovitis score (n=14).

Different sequences were observed. When the PD synovitis score was considered (n=23), 8 patients had a clinical relapse without a US relapse, 4 had a US relapse without a clinical relapse, 2 had a US relapse before a clinical relapse,

Table II. Clinical and ultrasonographic responses at each visit.

	Baseline	Months							
		4	6	8	10	12	14	16	18
Clinical response, n (%)									
Non responder	-	8 (27.6)	6 (21.4)	6 (23.1)	10 (41.7)	8 (32.0)	6 (26.1)	6 (27.3)	5 (25.0)
Responder	-	21 (72.4)	22 (78.6)	20 (76.9)	14 (58.3)	17 (68.0)	17 (73.9)	16 (72.7)	15 (75.0)
Response to intrasynovial PD score, n (%)									
Non responder	-	18 (62.1)	14 (50)	16 (61.5)	8 (33.3)	9 (36.0)	8 (34.8)	8 (34.8)	8 (42.1)
Responder	-	11 (37.9)	14 (50)	10 (38.5)	16 (66.7)	16 (64.0)	15 (65.2)	15 (65.2)	11 (57.9)
Response to composite PDUS score, n (%)									
Non responder	-	23 (79.3)	17 (60.7)	17 (65.4)	13 (54.2)	10 (40.0)	11 (47.8)	11 (47.8)	8 (42.1)
Responder	-	6 (20.7)	11 (39.3)	9 (34.6)	11 (45.8)	15 (60.0)	12 (52.2)	12 (52.2)	11 (57.9)

Table III. Correlation between changes in clinical /biological parameters and ultrasonographic parameters during the first 6 months of follow-up.

	TJC M0-M6	SJC M0-M6	GAS M0-M6	CRP M0-M6
M0-M6 changes in GS-assessed synovial hyperplasia global score				
r (CI 95%)	0.02 (-0.36; 0.39)	0.59 (0.27; 0.79)	0.20 (-0.19; 0.53)	0.19 (-0.20; 0.53)
p-value	0.92	**0.0007**	0.31	0.35
M0-M6 changes in intrasynovial PD signal global score				
r (CI 95%)	-0.04 (-0.40; 0.34)	0.59 (0.28; 0.79)	0.27 (-0.11; 0.59)	0.27 (-0.12; 0.59)
p-value	0.85	**0.0007**	0.15	0.17
M0-M6 changes in composite PDUS synovitis score				
r (CI 95%)	0.02 (-0.35; 0.39)	0.58 (0.26; 0.78)	0.20 (-0.19; 0.53)	0.20(-0.20; 0.54)
p-value	0.91	**0.0010**	0.31	0.32

r: Spearman rank correlation coefficient. CI 95%: 95% Confidence interval.
PD: power Doppler; TJC: tender joint count (/28 joints); SJC: swollen joint count (/28); GAS: global activity score evaluated by the patient; CRP: C-reactive protein.

Table IV. Ultrasonographic scores according to the clinical response observed at Month 6.

	Total population			No clinical response at Month 6			Clinical response Month 6		
	Baseline (n=29)	Month 6 (n=28)	Difference (n=28)	Baseline (n=6)	Month 6 (n=6)	Difference (n=6)	Baseline (n=22)	Month 6 (n=22)	Difference (n=22)
Score of grey-scale-assessed synovial hyperplasia, mean (SD)	17.3 (7.8)	10.4 (6.6)	-6.6 (6.4)	14.3 (9.3)	13.2 (8.3)	-1.2 (3.3)	17.7 (7.3)	9.6 (6.0)	-8.1 (6.3)
Score of intrasynovial power Doppler signal, mean (SD)	8.8 (5.2)	4.9 (4.3)	-3.5 (3.4)	10.2 (6.5)	8.0 (3.9)	-2.2 (3.1)	8.0 (4.6)	4.1 (4.1)	-3.9 (3.5)
Composite PDUS synovitis score, mean (SD)	17.6 (7.7)	10.5 (6.6)	-6.7 (6.5)	15.0 (9.3)	13.8 (8.0)	-1.2 (3.4)	17.8 (7.2)	9.6 (6.0)	-8.2 (6.3)

PDUS: power Doppler and grey-scale ultrasound.

and 4 had a clinical relapse before a US relapse. For 5 patients, both relapses were concomitant. Slight differences in terms of distribution were noted when the composite PDUS synovitis score was taken into account (n=20), notably 3 patients had a US relapse without a clinical relapse over the 18 months of follow-up (possibly occurring beyond this period) and 4 had a US relapse before a clinical relapse. Thus, from one quarter to one third of patients were characterised by a US relapse before a clinical relapse with the hypothesis that, for some of them, a new flare occurred beyond the follow-up period.

For the 19 patients with a clinical relapse (with or without a US relapse), 18 were retreated with rituximab during follow-up at a median of 49 days. Four of the seven patients without clinical or US relapse had rituximab retreatment, probably because they had low disease activity with a DAS 28 ESR between 2.6 and 3.2.

Only one of the three patients with a relapse evidenced only by ultrasonography (composite PDUS score) was retreated with rituximab (16 days after relapse).

Finally, whatever the US score used, 11 patients had a US relapse before retreatment (n=23)

All the data are summarised in Table V.

Discussion

This multicentre study is the first to evaluate, according to tight monitoring, changes in clinical symptoms and global PD-synovitis score in RA patients treated with rituximab over an 18-month follow-up. Although our study had some constraints such as the frequency of visits and examinations, the management of patients was left to the initiative of the investigator who was blind to US findings. Specifically, the time of retreatment was the decision of the clinical investigator which was based exclusively on clinical findings.

The characteristics of patients at baseline indicated active and longstanding RA as expected for a population with inadequate response to conventional DMARDs and at least one bDMARD. Thus, the mean disease duration was 12.4 (10.6) years and most patients had previously received bDMARDs (anti-TNF for 83% and abatacept for 21%). DAS28 mean score was 5.8 (1.4) and 5.2 (1.3) using ESR or CRP, respectively, thus indicating a very active disease in most patients.

For US monitoring of RA patients under treatment, the main parameter used in the present study was the global score of PD activity which is more sensitive than the global scores of synovial hyperplasia and composite PDUS synovitis to assess US changes over time as observed in previous studies (9, 12). Such an observation is particularly true for RA patients with longstanding disease, who represent the majority of the population studied here. A significant clinical and US response was observed at the first visit after rituximab treatment (Month 4) which continued to improve steadily over the 18-month follow-up. For the primary endpoint, the mean score of PD activity decreased from 8.8 (5.2) at baseline to 4.9 (4.3) at 6 months and 4.0 (3.6) at 18 months. A clinical and statistically significant improvement was also observed for GS-assessed synovial hyperplasia score, composite PDUS synovitis score and DAS28. The APPRAISE study was an

Table V. Different types of sequence of clinical relapse, US relapse and retreatment in this cohort of 29 RA patients treated by rituximab.

Patient	Clinical relapse (days)	Retreatment (Time of visit)	US relapse according to PD score (days)	Interval between clinical and PD score relapses (days)	Interval between PD score relapse and retreatment (days)	US relapse according to composite PDUS score (days)	Interval between clincal and composite PDUS score relapses (days)	Interval between composite PDUS score and retreatment (days)
1		No	442			442		
2	190	Yes (6 months)						
3		Yes (8 months)						
4		Yes (6 months)						
5	332	Yes (10 months)				177	- 155	182
6		No	326			326		
7	186	Yes (10 months)	186	0	107	186	0	107
8	207	Yes (10 months)	287	80	117			
9	203	Yes (8 months)	203	0	62			
10		No						
11	280	Yes (16 months)	280	0	175	280	0	175
12	350	Yes (12 months)	350	0	49	294	- 55	105
13	297	Yes (10 months)	238	- 59	59	297	0	0
14	185	Yes (10 months)	241	56	85	326	141	0
15		Yes (8 months)						
16	511	Yes (16 months)	231	- 280	297	336	- 175	192
17	210	Yes (8 months)	252	42	0	252	42	0
18	304	Yes (8 months)						
19		No						
20	196	No	266	70		266	70	
21	182	Yes (8 months)				266	84	0
22	190	Yes (8 months)						
23	280	Yes (8 months)						
24	244	Yes (12 months)	244	0	119	189	-55	174
25		Yes (8 months)	266		16	266		16
26		No	210					
27	252	Yes (10 months)						
28		Yes (8 months)						
29	244	Yes (8 months)						

6 patients were non-responders and 4 presented US relapse without clinical relapse

open-label single-arm study that evaluated abatacept in RA patients with inadequate response to methotrexate (9). The same composite PDUS synovitis score was used as in our study. The APPRAISE study showed that ultrasonography allowed to detect early improvements in the component scores: week 1 for PD signal, week 2 for synovial hyperplasia and week 4 for joint effusion. Nevertheless, in the present study, the ultrasonographic response was often delayed as compared to clinical response. This finding is in accordance with the fact that subclinical joint activity is long lasting in RA patients that are considered in clinical remission (12).

Retreatment with rituximab is generally necessary from 6 to 18 (sometimes 24) months after the initial injection (3). The present clinical trial was based on the suggestion that ultrasonography could be a useful tool to anticipate the reappearance of painful and disabling clinical symptoms in patients treated with rituximab. Indeed, due to long delays between the reappearance of symptoms and rheumatology appointments (most often 3 or 4 months), a new flare of RA is generally detected too late, which leads to increased doses of corticosteroids, alteration of quality of life, risk of progression of structural damage and risk of infections. The objective of our study was therefore to test the hypothesis that ultrasonographic signs of relapse may be present before clinical signs of relapse and might offer a window of opportunity for retreatment with rituximab, at least for some patients. We observed that 19 patients had a clinical relapse (regardless of ultrasonographic data) and, as expected, 18 of them were retreated with rituximab. Ten patients had no clinical signs of relapse but three of them had ultrasonographic signs of relapse. The relapse was evidenced for these three patients both on hypoechoic synovial hyperplasia using GS and on synovial vascularisation using PD. In addition, four patients had ultrasonographic signs of relapse before clinical relapse. In fact, besides this sequence of relapse, there was a great heterogeneity in the sequence of clinical/US relapses. Indeed, five scenarios were observed.

Only one of the three patients with ultrasonographic relapse but no clinical relapse was retreated. It should be noted that 7 patients were considered with no relapse (clinical or ultrasonographic) according to the study criteria. Nevertheless, four of them were retreated with rituximab. In the protocol, a clinical relapse was defined as DAS28 >3.2, but the final decision for retreatment was left to the clinical investigator who was blind to US data and some of them could have applied less stringent criteria. Indeed, these patients had low disease activity.

Our study has some limitations. The number of RA patients eligible for rituximab treatment who could be enrolled in the four centres over one year

was limited. Nevertheless, the number of included patients was based on sample size calculation with predefined statistical power and was considered to be adequate to reach the primary endpoint. This was indeed the case and the observed changes of clinical and ultrasonographic parameters were sufficiently large to reach statistical significance. The rate of discontinuation before assessing the primary endpoint was low and 29 out of the 30 enrolled patients could be analysed at 6 months. Because the study was open label, we cannot exclude a bias from patients and investigators who both expected clinical improvement. The use of ultrasonography even in open-label studies limits this pitfall. Thus, in our study, the investigators who performed joint ultrasonography were blind to the clinical and laboratory data. The study had a single arm and consequently only comparisons from baseline were performed and the improvement associated with rituximab itself could not be assessed as is the case in a comparative study. The aim of the study was however not to prove the efficacy of rituximab, but to evaluate in a real-life setting the interest of repeated ultrasonography examinations for RA management and retreatment.

Joint ultrasonography seems to display a greater interest in patients in sustained remission for whom PD signals could predict relapse when considering treatment tapering or withdrawal and after treatment discontinuation (13, 14).

Since ultrasonography has some limitations to detect clinical relapse in RA patients successfully treated with rituximab administered sequentially according to clinical findings, other approaches such as monitoring of B cell depletion or tight monitoring by nurse practitioners might be applied to predict clinical relapse (15, 16).

Until now, the optimal retreatment strategy for rituximab in RA patients has not been definitively determined. There are several options including retreatment based on occurrence of a new flare, regular retreatment, notably every 6 months, treatment to target. Regarding repeated courses of rituximab at 6-monts intervals, only the Study for Understanding Rituximab Safety and Efficacy (SUNRISE) trial has evaluated the efficacy of one versus two courses (baseline and week 24) of rituximab in patients with an inadequate response to at least one TNF inhibitor and demonstrated that re-treatment helps maintain disease control in responders at week 48 (17). However, we have no information about the safety with repeated courses of rituximab over a long period. Indeed, regular retreatment, regardless of the disease activity, might lead to overtreatment in some patients with an increased risk of infectious complications. Even though the mean time of retreatment has been estimated at around 8 months (18), the duration of the clinical response is variable and ranges from 4 to 24 months. Taking into account these different points, the consensus recommendations suggest rituximab retreatment for patients who did not achieve remission or low dose activity state after at least 6 months of infusion according to a treat-to-target strategy (19). The latter was applied in the present study thanks to a tight control of disease activity to attain low activity that is the therapeutic target in patients with longstanding RA refractory to at least one TNF-antagonist.

In conclusion, in this cohort of RA patients, a clinical relapse after rituximab treatment was most often associated with rituximab retreatment. Above all, this study highlights a great heterogeneity in the sequence of clinical relapse, US relapse and retreatment. Thus, according to this real-life study, US monitoring does not make it possible to detect a window of opportunity for rituximab retreatment before a new clinical flare.

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