Fluorescence optical imaging is helpful in the decision for rituximab (RTX) re-therapy in patients with rheumatoid arthritis

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Research article

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Abstract

Objective: To evaluate the ability of fluorescence optical imaging (FOI) Xiralite® in the prediction of RTX re-therapy in rheumatoid arthritis (RA) patients - in comparison to clinical, laboratory and musculoskeletal ultrasound (US) parameters.

Patients and methods: Patients with established RA were prospectively followed over one year by DAS28, patient's global disease activity (VAS 0-100 mm), CRP and ESR, US7 score and FOI in phases 1-3 and automatically generated PrimaVistaMode (PVM) at baseline (before RTX) and after 3, 6, and 12 months. The need for RTX re-therapy was decided by the treating rheumatologist – blinded to imaging data.

Results: 31 patients (female 77.4%, mean age 60.1±11.4, mean disease duration 14.9±7.1 years) were included. Fourteen patients (45.2%) received RTX re-therapy within 12 months. In the group with RTX re-therapy, FOI in PVM mode was the only parameter that presented significant increase over time (beta 0.40, CI 0.08-0.71; p=0.013) – compared to the group without re-therapy. In the prediction model via ROC analysis, FOI in PVM reached the highest values of all imaging, clinical and laboratory parameters for the prediction of re-therapy over one year with an area under the curve (AUC) of 0.78 (OR 0.84, CI 0.72;0.98, p=0.031). US7 GS synovitis score revealed similar predictive power with an AUC of 0.73 (p=0.049).

Conclusion: US7 GS synovitis score and FOI in PVM are able to discriminate between patients with and without need for RTX re-therapy better than clinical and laboratory parameters.

Introduction

Rheumatoid arthritis (RA) is a chronic multi-systemic autoimmune disease with a persistent inflammatory synovitis. The inflammation of the synovia leads to cartilage and bone destruction including bony erosions with consecutive joint deformities. In order to avoid corresponding complications, an effective therapy should be started immediately after a diagnosis of RA has been made (1). When conventional synthetic disease (csDMARDs) or TNF inhibitors operate inadequately or are not tolerated, Rituximab as a monoclonal anti-CD20 antibody can be applied (2, 3). The dosage for patients with RA is generally twice 1000mg, given at intervals of two weeks (2, 3). A re-therapy with RTX is recommended after 24 weeks if there has been an improvement of DAS28 more than 1.2 and either a residual disease activity (DAS28 > 3.2), or if a new increase of disease activity after initial response (increase of DAS28 > 0.6) has been observed (2, 4). Because of the subjective part of DAS28 (VAS) in decision-making (4), more objective methods for the decision of RTX re-therapy (e.g. imaging) are needed in order to detect subclinical disease activity and an upcoming flare before the patients will show clinical symptoms (5). Different imaging methods are applied including magnetic resonance imaging (MRI) and musculoskeletal ultrasound (US) which provide objective and reliable presentation of the current (sub)clinical disease activity (5-9). The US7 score includes the examination of seven preselected joints of the clinically dominant hand and forefoot by greyscale (GS) and power Doppler (PD). In a previously published study, a predictive value for re-therapy with RTX by using PDUS could be presented (5).

The fluorescence optical imaging (FOI) via the Xiralite® method detects disturbed microcirculation in the joints of both hands by using indocyanine green (ICG) (10-11, 13-14). Previous studies have shown a good correlation of FOI with MRI and US in synovitis detection (10-11, 13).

The current study aimed to analyse whether FOI is able to predict the need for re-therapy with RTX in RA-patients. To achieve this goal, FOI findings were compared to clinical, laboratory and US (US7 score) parameters.

Patients And Methods

The study was performed at the outpatient clinic of the department of Rheumatology and Clinical Immunology at the Charité –Universitätsmedizin Berlin, Germany. Ethical approval for the study was given by the ethical committee of the Charité – Universitätsmedizin Berlin, Germany (EA 1/193/10). Patients were included after written and oral consent. Inclusion criteria were a confirmed diagnosis of RA according to 2010 or 1987 criteria (15, 16), insufficient response to TNFα inhibitors, age ³ 18, psychological understanding of risk and side effects of the study and consent to participate in the study. The decision for re-therapy with RTX was made by the treating rheumatologist (SH) based on clinical judgement – independently of the knowledge of the imaging findings.

Clinical and laboratory parameters

Clinical investigation included the examination of tender and swollen joints (TJC-28 and SJC-28). DAS28(ESR) was calculated by additional application of patient's global VAS (0-100 mm) and erythrocyte sedimentation rate (ESR in hour/mm) before RTX-therapy and after 3, 6 and 12 months. Next to ESR, laboratory testing included C-reactive protein (CRP, normal <5.0 mg/l) before therapy with RTX, and after 3, 6 and 12 months. Furthermore, antibody status with Rheumatoid factor (RF-IgM, n<20 IU/ml) and anti-citrullinated antibodies (ACPA, n<20 IU/ml; both only at baseline) was assessed.

Musculoskeletal ultrasound examination (US7 score)

US examination (Esaote Mylab Twice (Genova; Italy)) using the US7 score (6) was performed before i.v. application of RTX (baseline), and after 3, 6 and 12 months. The US7 includes the investigation of the wrist (dorsal, palmar and ulnar), the metacarpophalangeal joints (MCP) 2 and 3, the proximal interphalangeal joints (PIP) 2 and 3 of the clinically dominant hand, and the metatarsophalangeal joints (MTP) 2 and 5 of the clinically dominant forefoot on dorsal and palmar/plantar sides by GS and PD mode. The standard performance of the US7 refers to the simultaneous evaluation of synovitis and tenosynovitis (5-8). All included joints (except the wrist) were also examined from dorsal and palmar/plantar for erosions, additionally MCP2 from radial and MTP5 from lateral (5-8). Synovitis was assessed semiquantitatively (0 = synovitis not existing, 1 = mild, 2= moderate, 3 = severe synovitis) (18). Tenosynovitis and erosions were evaluated if they were present (= 1) or not (= 0) (10).

The semiquantitative diagnostic findings for PD activity for synovitis were evaluated according to Szkudlarek *et al.* in the following way (10):

- Grade 0 = no color signal
- Grade 1 = up to three color signals or two and one confluent color signal in the intraarticular area
- Grade 2 = more than three color signals which filled less than 50% of the intraarticular area
- Grade 3 = more than 50% of the intraarticular area was filled with color signals.

Fluorescence optical imaging (FOI)

Fluorescence optical imaging was performed by the Xiralite 4 system (Xiralite GmbH, Berlin; Germany). FOI images were taken before the beginning of RTX- therapy and after 3, 6 and 12 months in a standardized manner. Ten seconds after start of the procedure, a bolus of 0,1 mg/kg/body weight of the fluorescent dye indocyanine green (ICG) was applied intravenously. The examination lasted six minutes recording one image per second adding up to a cluster of 360 images. The examination included 30 joints of both hands (the wrist, MCP-, PIP-, (D)IP-joints of both hands) (11-13). The analyses of the images referred to evaluation of the first 240 images forming the automatically generated PrimaVistaMode (PVM) (11-13). In addition, three phases in position to the fingertips with regard to development of signal intensities were defined and analysed (11-13). **Phase 1** includes the period between starting the investigation, application of the dye and increased signal intensities in the fingertips; the last image before the dye leaves the fingertips (in yellow or in red or in white – not in green) from distal to proximal in wrist direction was used for scoring. **Phase 2** begins when the dye leaves the fingertips from distal to proximal in wrist direction and stops when only red colour in the fingertips is visible; the first image with red colour in the fingertips (no white anymore) was used for the scoring. **Phase 3** begins when only yellow dots or no signal intensity can be seen in the fingertips; the first image without red dots in the fingertips was used for the scoring.

The adjustment of the phases and their evaluations were performed for every wrist and single finger separately. The evaluation was performed semiquantitatively in the following way taking into account size, form and color of the concentration of ICG (11-13):

- **Grade 0** = no signal enhancement,
- **Grade 1** = enhancement varies from yellow to red and can reach red with yellow spots, red covers ≤50% of the enhanced/affected joint area,
- **Grade 2** = the signal intensity shows strong red colour intensity and can also include white signals, white covers ≤50% of the enhanced/affected joint area,
- **Grade 3** = the signal intensity shows white colour intensity, white covers >50% of the enhanced/affected joint area[1]

Statistical analysis

Standard descriptive statistics were used to report patients' characteristics and the course of clinical, ultrasound and FOI parameters at each visit within 12 months. The change of disease activity parameters, US7 scores and FOI across 12 months was analyzed by generalized linear mixed models for the total sample and separately for patients with and without RTX re-therapy through follow-ups. Mann Whitney U-test was used to compare the parameters between patients with and without RTX re-therapy at each visit. The association between disease activity parameters, US7 scores and FOI was investigated by Spearman's correlation coefficients. Furthermore, logistic regression analyses were conducted to model the likelihood for a re-therapy with RTX within 12 months by DAS28, US7 score and FOI. The area under the curve (AUC) was estimated after fitting the logistic regression model to assess the predictive value for each parameter for re-therapy with RTX. The level of significance was defined by $\alpha < 0.05$. The statistical analysis was conducted in STATA 12.1.

Results

Total patient group

Thirty-one patients were examined at baseline, n=29 after 3 and n=28 after 6 and 12 months (3 patients lost to follow-up). The patients included (24 females) revealed a mean age of 60.1±14.9 years and mean disease duration of 14.9±7.1 years. 96.8% of the patients were rheumatoid factor (RF-IgM) positive and 93.6% ACPA positive.

Regarding prior treatment, 28 patients had received other biologicals (TNFα- or IL6- inhibitors). Reasons for discontinuing previous drug treatment were nonresponse (40.0%), insufficient effectiveness (46.7%), contraindications (16.7%) and adverse events (46.7%). 17 patients had already received Rituximab before being included in the study.

Additionally, concomitant therapies such as NSAIDs, glucocorticoids and DMARDs were used by all patients within one year as follows: NSAIDs: at baseline: 71.0% (n=22), after 12 months: 64.3% (n=18); Glucocorticoids (prednisone equivalent): at baseline: 87.1% (mean daily dosage à 7.4 mg), after 12 months 75% (mean daily dosage à 4.9 mg); DMARDs (mostly methotrexate, followed by: leflunomide, sulfasalazine, hydroxychloroquine, azathioprine): 61.3%, after 12 months 50.0%.

In the *total study population*, mean DAS28 decreased from 5.1±1.2 to 4.3±1.1 (p= 0.003) and mean patient's global VAS (range 0-100mm) from 54.8±17.2 to 41.3±16.2 (p=0.001), respectively. Mean CRP was significantly reduced from 10.7±9.6 to 5.7±8.0 (p=0.023) over the period of 12 months.

The imaging parameters US7 GS synovitis score (range 0-27) and US7 GS tenosynovitis score (range 0-7) presented a significant decrease during one year (mean 13.3±7.7 to 9.7±6.6; p=0.005 and mean 1.4±1.6 to 0.8±1.2; p=0.008).

FOI in PVM increased in a course of 12 months (mean 9.8±6.9 to 13.2±9.8, p=0.111), while FOI in phases 1, 2, and 3 decreased (phase 1: mean 9.1±11.1 to 4.8±9.7, p=0.704, phase 2: mean 31.8±15.2 to

30.1±15.6, p=0.182, phase 3: mean 10.4±8.6 to 9.0±7.2, p=0.537) not significantly (**Supplementary Table 1**).

Patients with RTX re-therapy

Of the total 31 patients, n=14 received a re-therapy with RTX (45.2%) within 12 months: n=3 after 6 months, n=4 after 7 months, n=5 after 9 months, and n=2 after 10 months. The parameters DAS28 and patient's global VAS decreased significantly in this group (mean of DAS28 at baseline 5.1, after 12 months 3.9; p=0.004; mean patient's global VAS at baseline 59.6mm, after 12months 45mm; p=0.042).

FOI in PVM singularly significantly increased (mean 7.8±4.3 to 15.2±10.4; p=0.013; range 0-90) in comparison to the other imaging parameters (see **Table 1**).

Prediction for RTX re-therapy

The likelihood for a RTX re-therapy (after 6 months) was analyzed by considering the predictive value of the change between baseline and 3-months or 6-months follow-up in clinical and patient reported parameters. The change in DAS28, ESR and CRP as well as patient reported parameters were not associated with the initiation of a RTX re-therapy (AUC close to 0.5). On the other side, the likelihood of a RTX re-therapy was significantly predicted by the change between baseline and 6-months follow-up in the imaging parameters US7 GS synovitis score (AUC = 0.73) and FOI in PVM (AUC = 0.78). (see **Table 2**).

Patients without RTX re-therapy

Seventeen patients of the total patient group did not receive a re-therapy with RTX during the observed 12 months. In this group, a significant decrease between baseline and 12-months follow-up was shown for the patient's global VAS, US7 GS synovitis, US7 GS tenosynovitis, US7 PD tenosynovitis, and FOI in phase 2. (**Table 1**). However, the clinical parameters did not change significantly in this group. The ESR after 12 months was significantly higher than in the group with re-therapy (p=0.033). Regarding FOI, signal enhancement in phase 2 was reduced in a significant manner (mean 33.9±15.8 to 28.2±17.3; p=0.008). PVM remained stable in this group.

Discussion

The aim of this study was the evaluation of FOI for its capacity to predict the need for RTX re-therapy in RA patients- in comparison to clinical, laboratory and musculoskeletal ultrasound (US7 score) parameters. In this study, FOI was for the first time evaluated to determine its predictive value for RTX re-therapy.

The clinical and laboratory parameters DAS28, patient's global VAS and CRP decreased significantly over one year under RTX-therapy in all patients. A decrease of the US7 synovitis and tenosynovitis GS scores was also evident. This was already described in the study by Reiche *et al.*, in which the US7 GS synovitis

and erosions scores showed a significant decrease in all examined patients under RTX therapy after one year. All these decreased parameters thereby represent a response to RTX (2, 5).

All patients received DMARDs additionally to RTX according to EULAR recommendations (2). Moreover, all patients (except one) were positive for RF and ACPA. This aspect corresponds with the results of previous studies, in which a high RTX response after an insufficient response to TNFα inhibitors was demonstrated in RF- and ACPA-positive patients (17).

Due to the residual disease activity of DAS28 of more than 3.2 and taking physician's statement into account, 14 patients received a re-therapy with RTX according to consensus agreement (2) in this one-year follow-up study. In the group of RTX re-therapy, DAS28 and patient's global VAS decreased significantly, and also the US7 score parameters decreased, though with no significance. This could also be observed in the study by Reiche *et al.* in which the number of swollen joints and laboratory parameters decreased significantly after 6 months and also the US7 scores decreased after 6 months without significance. In contrast to the study by Reiche *et al.,* US7 synovitis score by PD did not show an increase from baseline up to 6 months later. But the US7 synovitis score by GS was -in addition to FOI in PVM- the only parameter in our analyses, which was able to discriminate between groups with and without the need for RTX re-therapy.

US7 GS synovitis score and FOI in PVM showed a significant signal increase before clinical symptoms became obvious in the group of RTX re-therapy. These were the only parameters with a power to predict the need for re-therapy with RTX in RA patients.

To our knowledge, this result of missing clinical activity and obvious FOI activity in the means of a prediction of flare has not been shown in previous studies investigating FOI. However, a detection of subclinical activity in FOI phase 2 has already been discussed by Werner *et al.* (13). The current results may give FOI an important value for recognizing disease activity before patients exhibit clinical signs of flare. Due to the automatic production of a total screen in PVM, it is a more objective and rapidly practicable method for the evaluation of disease activity. If FOI in PVM continues proving as a predictor for RTX re-therapy, it would be a good objective method in everyday clinical practice. The adjustment of the phases 1-3 in FOI and their evaluation for every wrist and single finger separately allows a precise estimation of disease activity; however, these phases do not appear to be meaningful for the prediction of re-therapy to RTX according to the present results. Overall, the evaluation of the automatic PVM might save a lot of time since it is the quickest method in the systematic FOI evaluation due to its automatic production by the Xiraview® Software.

In conclusion, it can be stated that FOI in PVM and also US7 GS synovitis are able to discriminate between groups with and without need for RTX re-therapy better than other included imaging, clinical and laboratory parameters. At the same time, FOI is a more objective tool, while DAS28, patient's VAS, CRP and ESR can also depend on other influence (i.e. psychological, infectious, contraceptives, hyperlipoproteinemia, hemoglobin value) factors. Consideration should therefore be given to including

objective factors such as FOI in PVM in the decision on RTX re-therapy. In order to fully consolidate these results, further FOI studies on larger scales are required.

Declarations

Ethics approval and consent to participate

The local ethics committee of the Charité – Universitätsmedizin Berlin, granted ethical approval (reference no. EA1/193/10). Signed informed consent to participate was obtained from all patients.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

All authors participated in the preparation of the manuscript. SLRA, AMG, SO contributed to the study design, data acquisition and analysis, and drafting of the manuscript. GRB, PH, GS, MB contributed to the study design and manuscript revision. SH contributed to the data acqusition and manuscript revision SH JK contributed to the data analysis and manuscript revision. All authors read and approved the final version of the manuscript.

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Tables

Table 1: Changes of clinical, laboratory, US and FOI parameter over 12 months after RTX therapy in patients with and without re-therapy

	Patients with RTX re-therapy (n=14)			Patients without RTX re-therapy (n=17)		
	Baseline	12-months follow-up	β 95% CI p-value+	Baseline	12-months follow-up	β 95% CI p-value+
DAS28	5.1 ± 1.0 (5.0)	3.9 ± 0.8 (4.0)	-0.08 -0.13 ;-0.03 0.004*	5.1 ± 1.3 (5.2)	4.7 ± 1.2 (4.7)	-0.03 -0.08 ;0.01 0.172
Patient global VAS	59.6 ± 14.1 (60.0)	45.0 ± 13.0	-1.01 -1.98 ;-0.04 0.042*	49.0±19.3 (50.0)	37.5 ± 18.6 (37.5)	-1.05 -1.92 ;-0.19 0.016*
ESR	28.6 ± 22.5 (25.0)	17.6 ± 9.0 (16.0)	-0.46 -1.32 ;0.40 0.293	38.1 ± 23.7 (30.0)	37.7 ± 25.9 (33.0)	-0.07 -0.80 ;0.67 0.860
CRP	7.5 ± 8.4 (4.1)	4.4 ± 5.0 (2.0)	-0.35 -0.84 ;0.13 0.153	13.1 ± 9.5 (14.8)	7.0 ± 10.1 (2.2)	-0.30 -0.68 ;0.09 0.132
US7 GS synovitis	12.7 ± 6.6 (12.0)	10.6 ± 6.9 (9.0)	-0.06 -0.24 ;0.12 0.507	12.8 ± 7.6 (12.0)	8.7 ± 6.5 (7.0)	-0.31 -0.50 ;-0.12 0.001*
US7 GS tenosynovitis	1.1 ± 1.3 (0.5)	0.9 ± 1.2 (0.5)	0.001 -0.04 ;0.04 0.955	1.5 ± 1.8 (1.0)	0.6 ± 1.2 (0.0)	-0.06 -0.10 ;-0.01 0.009*
US7 PD synovitis	4.3 ± 3.0 (3.5)	3.2 ± 4.3 (1.5)	-0.05 -0.18 ;0.07 0.423	4.3 ± 5.0 (4.0)	2.4 ± 3.1 (1.0)	-0.12 -0.25 ;0.02 0.101
US7 PD tenosynovitis	0.7 ± 1.6 (0.0)	0.4 ± 0.7 (0.0)	-0.02 -0.06 ;0.03 0.509	1.6 ± 3.0 (0.0)	0.6 ± 2.1 (0.0)	-0.07 -0.12 ;-0.02 0.010*
US7 erosions	3.3 ± 2.5 (3.0)	3.3 ± 2.4 (3.0)	-0.02 -0.07 ;0.04 0.491	3.2 ± 2.6 (3.0)	2.6 ± 2.2 (2.0)	-0.03 -0.08 ;0.01 0.093
FOI PVM	7.8 ± 4.3 (7.5)	15.2 ± 10.4 (13.0)	0.40 0.08 ;0.71 0.013*	12.1 ± 8.6 (11.5)	11.1 ± 9.1 (9.0)	-0.13 -0.33 ;0.07 0.209
FOI P1	8.4 ± 10.2 (4.5)	5.5 ± 10.4 (1.0)	-0.11 -0.48 ;0.26 0.574	8.8 ± 11.1 (6.0)	4.0 ± 9.3 (0.0)	-0.11 -0.59 ;0.37 0.650
FOI P2	29.6 ± 12.2 (29.0)	31.9 ± 14.4 (32.0)	0.11 -0.16 ;0.37	33.9 ± 15.8 (33.5)	28.2 ± 17.3 (29.0)	-0.46 -0.80 ;-0.12

			0.436			0.008*
FOI P3	10.1 ± 7.9 (9.0)	9.8 ± 7.9 (12.0)	-0.02 -0.24 ;0.21 0.876	9.9 ± 7.4 (10.0)	8.2 ± 6.8 (8.0)	-0.13 -0.36 ;0.11 0.296

Mean ± standard deviation (median); 95% confidence interval (12 months column); beta as change after 12 months (12 months column); +p-value for significant change over time; DAS28 = Disease Activity Score 28; VAS = Visual analogue scale (0-100mm); CRP = C-reactive protein (mg/l); ESR = Erythrocyte sedimentation rate (mm/hour); US7 = Ultrasound seven joint score; GS = Greyscale; PD = power Doppler; FOI = Fluorescence Optical Imaging; PVM = Prima Vista Mode; P1,2,3 = FOI phases 1,2,3.

Table 2: Changes between Baseline and 6-months follow-up

Parameters	OR	AUC	95% Cl	p-value
DAS28	1.04	0.48	0.57;1.93	0.889
Patient global VAS	1.02	0.63	0.99;1.04	0.301
ESR	1.00	0.51	0.96;1.04	0.952
CRP	0.98	0.58	0.89;1.07	0.587
US7 score for GS synovitis	0.82	0.73	0.67;1.0	0.049
FOI in PVM	0.84	0.78	0.72;0.98	0.031

Legend: DAS28 = Disease Activity Score 28; VAS = Visual analogue scale (0-100mm); CRP = C-reactive protein (mg/l); ESR = Erythrocyte sedimentation rate (mm/hour); US7 = Ultrasound seven joint score; GS = Greyscale; FOI = Fluorescence Optical Imaging; PVM = Prima Vista Mode

Figures

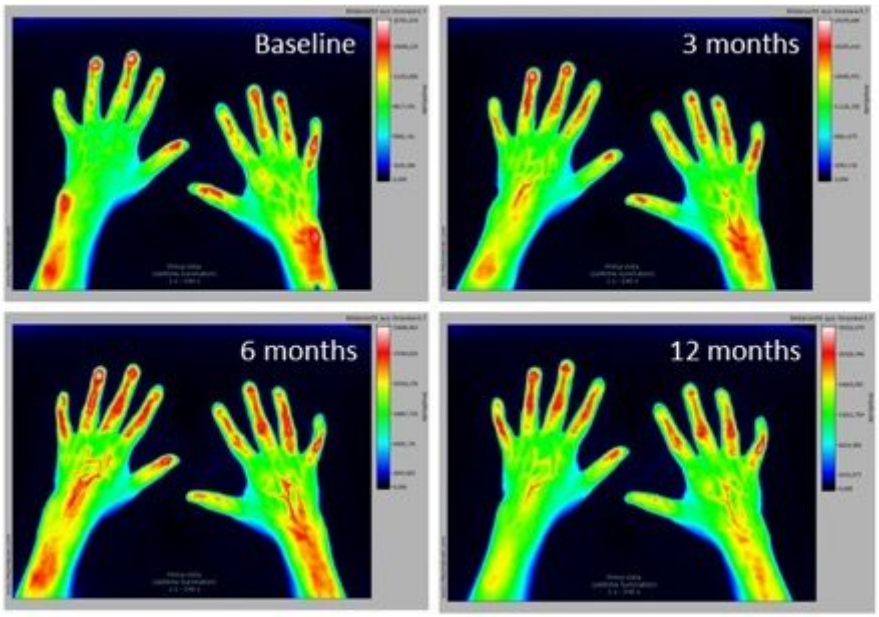

Figure 1

Fluorescence Optical imaging (FOI) in follow up with 12 months after RTX therapy. At baseline, moderate enhancement in both wrists decreasing within 12 months. FOI: Fluorescence optical imaging; PVM: Prima Vista Mode; RTX: rituximab.

Supplementary Files

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- SupplementaryTableS1andFigureS120200315.docx