

ORIGINAL ARTICLE

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## Doppler ultrasound measurements of knee joint synovitis in rheumatoid arthritis patients treated with infliximab

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**Abstract** Doppler ultrasound measurements were done for the thickness of synovial effusion and synovial proliferation (pannus), and diameter of the flow signals using digital calipers as well as flow signal grades and vascular resistance in the knee joint synovitis of patients with rheumatoid arthritis (RA) treated with infliximab. Forty knee joints of 20 RA patients were assessed before and after three injections of infliximab. The flow signals in the pannus were classified into the superficial and the deep signals and the joints were classified into the superficial signal pattern and the deep signal pattern. After treatment, the number of joints with superficial signal pattern reduced from 23 to 11, whereas the number of joints with deep signal pattern increased from 17 to 29 ( $P = 0.0066$ ), with a significant reduction of the superficial signal grades ( $P = 0.0003$ ). The mean cortical (posterior) pannus thickness increased significantly in the joints with superficial signal pattern ( $P = 0.022$ ) and in the total joints (superficial plus deep signal pattern) ( $P = 0.031$ ) but not in the joints with deep signal pattern. After 6 weeks of treatment with infliximab, the hyperemia in the superficial layer of the pannus developed into proliferation of the cortical pannus in the knee joints.

**Key words** Capsular pannus · Cortical pannus · Deep flow signal · Superficial flow signal · Ultrasound measurements

### Introduction

Doppler ultrasonography on synovitis in rheumatoid arthritis (RA) patients treated with tumor necrosis factor alpha (TNF $\alpha$ ) blockades has been successfully applied to evaluation of the therapeutic response of the patients.<sup>1–8</sup> In those studies, the thickness of the synovial proliferation and synovial effusion was evaluated by either measurement in millimeters<sup>2,3,5</sup> or semiquantitative grading (0 to 3).<sup>4,6</sup> In a previous report in *Modern Rheumatology*,<sup>9</sup> we presented a Doppler ultrasound study using digital calipers to measure in mm knee joint synovitis in rheumatoid arthritis (RA) patients. In that study, there were significant differences in effusion thickness, signal diameter, flow signal grades, and vascular resistance index (RI) between joints that had superficial pattern signals and those that had deep pattern signals. Therefore, we reassessed by millimeter measurements the ultrasound findings of knee joint synovitis, classifying them into superficial and deep signal patterns, in 20 RA patients treated with infliximab; 12 of those 20 patients were previously reported in a study published in this journal<sup>6</sup> dealing with semiquantitative grading (0 to 3) of their ultrasound findings.

### Patients and methods

#### Patients

All 20 patients (15 women and 5 men with a mean age of 43.2 years and a mean disease duration of 6.8 years) satisfied the American College of Rheumatology 1987 revised criteria<sup>10</sup> and the official Japanese guidelines for the use of infliximab in rheumatoid arthritis.<sup>11</sup> Forty knee joints were assessed by Doppler ultrasonography before and after 3 injections (0, 2, 6 weeks) of infliximab (3 mg/kg). The DAS28-E3 disease activity score was calculated based on values of number of tender and swollen joints and erythrocyte sedimentation rate.

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## Methods

Doppler ultrasonography was done as described in our previous report<sup>9</sup> using the pulse repetition frequency with 1170–1220 Hz for power Doppler, and the lowest filter setting with 125 Hz for spectral Doppler. For each patient, both knees were scanned longitudinally and transversely at the suprapatellar recess. The flow signals were graded (0 to 3) using the modified Klauser method<sup>12</sup> and were classified as belonging to either the superficial signals (located in the superficial half of the pannus and the fluid space) or the deep signals (located in the deep half of the pannus). Subsequently, the joints were classified into those joints with superficial signal pattern and those with deep signal pattern based on the dominant location of the flow signals in the pannus in taking together both the longitudinal and transverse scan findings. For each joint, the pannus was classified into the anterior (capsular) pannus and the posterior (cortical) pannus, based on their location attaching to the articular capsule or the femoral cortex. Using digital calipers, the thicknesses (in mm) of the effusion and the pannus, as well as the signal diameter, were measured on the ultrasonogram prints. The resistance index (RI) value was calculated by the following formula: maximum velocity–minimum velocity/maximum velocity. For statistical analysis, the Wilcoxon signed rank sum test was used to calculate the paired data and the Mann–Whitney *U*-test was used to calculate the unpaired data.

## Results

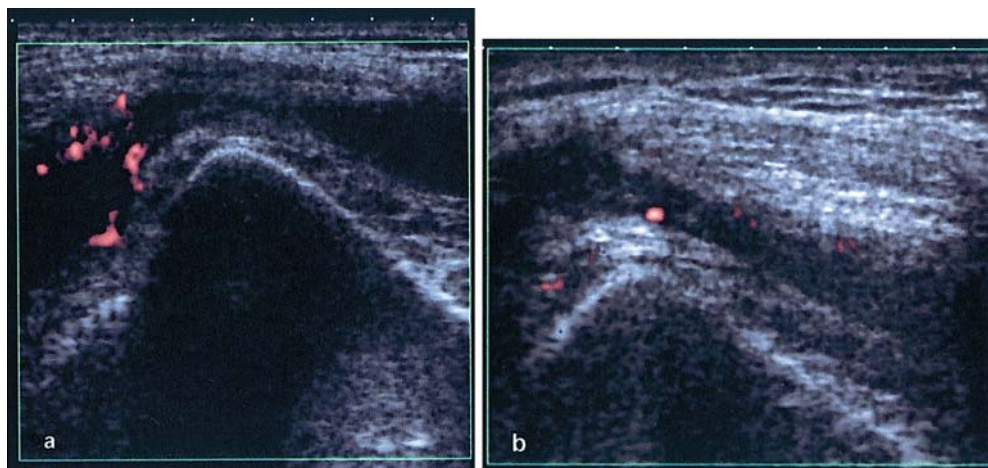
Doppler ultrasonograms taken in two patients are shown in Figs. 1 and 2. The first patient is a 51-year-old woman with

a disease duration of 13 years. The images taken on the right knee joint before and after 3 infliximab injections are shown in Fig. 1a and b. In parallel to the clinical improvement with a reduction of DAS28-E3 value from 5.72 to 3.98, the grade of the superficial signals was reduced from 3 to 1. Similarly, the effusion thickness was reduced from 4.98 to 3.31 mm. However, the thickness of the pannus, signal diameter, and RI values did not show a great change except capsular pannus thickness. The second patient is a 60-year-old man with a disease duration of 1.5 years. The images taken on the left knee joint of this patient before and after 3 infliximab injections are shown in Fig. 2a and b. The same two images were evaluated by the semiquantitative grading used in the previous study.<sup>6</sup> In parallel to the clinical partial improvement after the therapy with a mild reduction of DAS28-E3 value from 6.13 to 5.16, grades of the superficial signals were reduced from 3 to 2. The effusion thickness was reduced slightly from 8.58 to 7.52 mm and these two values were previously evaluated as the same grade 2 by the semiquantitative method. The cortical pannus thickness was reduced slightly from 8.83 to 5.79 mm and these two values were evaluated in the previous study as grade 2 and grade 1, respectively. The results obtained in 20 patients with mean  $\pm$  SD values are summarized in Table 1. As shown in Table 1, DAS28-E3 values were significantly reduced ( $P < 0.0001$ ) after therapy. The superficial signal grades were significantly reduced ( $P = 0.0003$ ), whereas the deep signal grades tended to increase, but this trend was not significant ( $P = 0.087$ ). The number of joints with a superficial signal pattern decreased from 23 to 11 after therapy, whereas the number of joints with a deep signal pattern increased from 17 to 29 after therapy; the correlation between these binary data was statistically significant ( $P = 0.0066$  by chi-squared test). The mean effusion thickness tended to decrease after therapy, but this was not significant ( $P =$

**Table 1.** Ultrasound measurements of 40 knee joints in 20 rheumatoid arthritis patients treated with infliximab

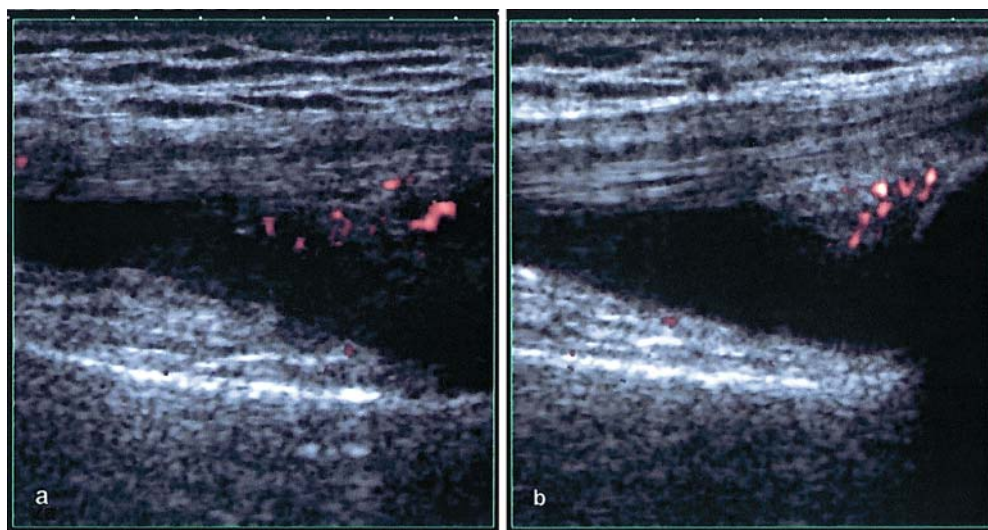
Ultrasound measurements	Pretreatment (mean $\pm$ SD)	After 3 infliximab injections (mean $\pm$ SD)	<i>P</i> value
DAS28-E3	5.72 $\pm$ 0.59****	4.14 $\pm$ 0.50	<0.0001
Joint signal grades ( <i>n</i> = 40)			
Superficial signals	1.33 $\pm$ 1.07***	0.70 $\pm$ 0.82	0.0003
Deep signals	0.68 $\pm$ 0.47 n.s.	0.88 $\pm$ 0.56	0.0867
No. of joints with			
Superficial signal pattern (a)	23	11	(0.0066)**
Deep signal pattern (b)	17	29	
Effusion thickness (mm)			
(a) + (b)	5.22 $\pm$ 2.58 n.s.	4.29 $\pm$ 2.31	0.0929
Pannus thickness (mm)			
Capsular pannus			
(a) + (b)	8.33 $\pm$ 2.12 n.s.	7.91 $\pm$ 2.07	0.5364
Cortical pannus			
(a)	6.02 $\pm$ 1.78*	7.35 $\pm$ 1.13	0.0224
(b)	6.61 $\pm$ 2.16 n.s.	7.29 $\pm$ 2.52	0.5389
(a) + (b)	6.27 $\pm$ 1.94*	7.30 $\pm$ 2.21	0.0305
Total pannus	14.59 $\pm$ 3.13 n.s.	15.21 $\pm$ 3.45	0.3399
Signal diameter (mm)			
(a) + (b)	1.29 $\pm$ 0.32 n.s.	1.31 $\pm$ 0.31	0.5101
Resistance index (RI)			
(a) + (b)	0.79 $\pm$ 0.12 n.s.	0.82 $\pm$ 0.12	0.1046

\* $P < 0.05$ ; \*\* $P < 0.01$ ; \*\*\* $P < 0.001$ ; \*\*\*\* $P < 0.0001$ ; n.s., not significant; ( ) chi-squared test



**Fig. 1.** Doppler ultrasonograms of the right knee joint of the first patient scanned transversely on the suprapatellar recess before (a) and after 3 infliximab injections (b). **a** Joint signal grade, 3 for superficial signal and 0 for deep signal; signal pattern superficial; effusion thickness, 4.98 mm; capsular pannus thickness, 5.53 mm; cortical pannus thickness, 4.37 mm; diameter of one of the cortical superficial signals, 0.81 mm; resistance index (RI) of the corresponding signal to that

selected for the diameter measurement, 0.63. **b** Joint signal grade, 1 for superficial signal and 1 for deep signal; signal pattern, superficial; effusion thickness, 3.31 mm; capsular pannus thickness, 9.25 mm; cortical pannus thickness, 4.45 mm; diameter of one of the capsular superficial signals, 0.79 mm; RI of the corresponding signal to that selected for the diameter measurement, 0.67. The scale on the top of the figure is marked in 5 mm



**Fig. 2.** Doppler ultrasonograms of the left knee joint of the second patient scanned longitudinally on the suprapatellar recess before (a) and after 3 infliximab injections (b). **a** Joint signal grade, 3 for superficial signal and 0 for deep signal; signal pattern, superficial; effusion thickness, 8.58 mm; capsular pannus thickness, 10.0 mm; cortical pannus thickness, 8.83 mm; diameter of one of the capsular superficial signals, 0.96 mm; RI of the corresponding signal to that selected for the diam-

eter measurement, 0.75. **b** Joint signal grade, 2 for superficial signal and 0 for deep signal; signal pattern superficial; effusion thickness, 7.52 mm; capsular pannus thickness, 12.04 mm; cortical pannus thickness, 5.79 mm; diameter of one of the capsular superficial signals, 1.22 mm; RI of the corresponding signal to that selected for the diameter measurement, 0.78. The scale on the top of the figure is marked in 5 mm

0.093). The post-treatment mean capsular pannus thickness was similar to the pre-treatment value. However, the mean cortical pannus thickness increased significantly in the joints with superficial signal pattern from 6.02 to 7.35 mm ( $P = 0.022$ ) and also in the total joints (superficial plus deep signal pattern) from 6.27 to 7.30 mm ( $P = 0.031$ ), but not in the joints with deep pattern signals after treatment. The post-treatment mean value of total (capsular plus cortical) pannus thickness was similar to the pretreatment value. There were no significant changes in mean signal diameter and RI following treatment. In either joints with the super-

ficial signal pattern or those with the deep signal pattern, there was no significant change in mean values of the effusion thickness, capsular pannus thickness, signal diameter, and RI after treatment.

## Discussion

The present results indicate a shift in knee joint signal patterns with therapy from a superficial signal pattern to a deep

signal pattern along with a significant reduction in superficial signal grades, and showed a significant increase in cortical pannus thickness, especially of the joints with superficial signal pattern. These observations are in agreement with previous results showing that deep signal pattern joints had lower signal grades and a trend to greater pannus thickness compared to superficial signal pattern joints.<sup>9,13</sup> The association between the reduction of the superficial signal and the increase of cortical pannus thickness of the joints with superficial signal pattern following treatment might be explained by a remodeling process in the superficial tissue of the pannus, which changes from hyperemic inflammation to fibrous proliferation with infliximab treatment. However, it is unclear why the thickness of the cortical pannus increased while that of the capsular pannus did not. As was demonstrated in the second patient presented in the results, there are several differences in the evaluation of the results between the present quantitative evaluation (in mm) and the previous semiquantitative evaluation (scores, 0 to 3) for infliximab treatment<sup>6</sup>: the *P* value difference in effusion thickness (0.093 and 0.0046, respectively) and the contradictory results showed a significant increase in the cortical pannus thickness in the present study (*P* = 0.031), whereas a significant decrease in the pannus (cortical) thickness was detected in the previous study (*P* = 0.039) after the treatment.<sup>6</sup> Those differences may be due to the different evaluation methods (quantitative vs semiquantitative) and the difference in the number of the subjects studied (20 vs 12). Ultrasonographic measurements in millimeters of synovial effusion and synovial proliferation will provide more precise information than grading methods on the therapeutic response of the patients to the quickly effective drugs such as TNF $\alpha$  blockades. The observed results on significant reduction in the grades of the superficial signals with a shift of the signal pattern from superficial to deep are in agreement with those reported by Fiocco et al.,<sup>5</sup> in which a significant reduction in grades of the superficial signals but not of the deep signals was shown after 3-month injection of etanercept. Therefore, the classification of the flow signals in the joints into the superficial and deep signal pattern will provide more precise information on the responsiveness of the patients who received drugs.

In conclusion, the ultrasound measurement of knee joint synovitis provides more precise information on evaluating effusion and pannus thickness in RA patients. After 6 weeks of infliximab therapy, RA patients developed a significant shift in the knee joint signal pattern from the superficial pattern to the deep pattern, with a significant reduction of the superficial signal grades, and showed a significant increase in cortical pannus thickness.

## References

- Hau M, Kneitz C, Tony H-P, Keberle M, Jahns R, Jenett M, et al. High resolution ultrasound detects a decrease in pannus vascularization of small finger joints in patients with rheumatoid arthritis receiving with soluble tumor necrosis factor  $\alpha$  receptor (etanercept). *Ann Rheum Dis* 2002;61:55–8.
- Ribbens C, Andre B, Marcelis S, Kaye O, Mathy L, Bonnet V, et al. Rheumatoid hand joint synovitis: gray-scale and power Doppler US quantifications following anti-tumor necrosis factor  $\alpha$  treatment: pilot study. *Radiology* 2003;229:562–9.
- Terslev L, Torp-Pedersen S, Qvistgaard E, Kristoffersen H, Rogind H. Effect of treatment with etanercept (Enbrel, TNRF:Fc) on rheumatoid arthritis evaluated by Doppler ultrasonography. *Ann Rheum Dis* 2003;62:178–81.
- Taylor PC, Steuer A, Gruber J, Cosgrove DO, Blomley MJK, Marsters PA, et al. Comparison of ultrasonographic assessment of synovitis and joint vascularity with radiographic evaluation in a randomized, placebo-controlled study of infliximab therapy in early rheumatoid arthritis. *Arthritis Rheum* 2004;50:1107–16.
- Fiocco U, Ferro F, Vezzu M, Cozzi L, Checchetto C, Sfriso P, et al. Rheumatoid and psoriatic knee synovitis: clinical, gray-scale and power Doppler ultrasound assessment of the response to etanercept. *Ann Rheum Dis* 2005;64:899–905.
- Kanno Y, Homma F, Takahashi A, Sato A, Yamadera Y, Ohguchi Y, et al. Doppler sonographic evaluation of infliximab therapy for rheumatoid arthritis. *Mod Rheumatol* 2005;15:305–6.
- Shio K, Homma F, Kanno Y, Yamadera Y, Ohguchi Y, Nishimaki T, et al. Doppler sonographic comparative study on usefulness of synovial vascularity between knee and metacarpophalangeal joints for evaluation of articular inflammation in patients with rheumatoid arthritis treated by infliximab. *Mod Rheumatol* 2006;16:220–5.
- Filippucci E, Iagnocco A, Salaffi F, Cerioni A, Valesini G, Grassi W. Power Doppler sonography monitoring of synovial perfusion at the wrist joints in patients with rheumatoid arthritis treated with adalimumab. *Ann Rheum Dis* 2006;65:1433–7.
- Kasukawa R, Shio K, Kanno Y, Sato A, Takahashi A, Yamadera Y, et al. Power Doppler and spectral Doppler measurements of knee joint synovitis in rheumatoid arthritis patients with superficial pattern signals and in those with deep pattern signals. *Mod Rheumatol* 2007;17:267–72.
- Arnett FC, Edworthy SM, Block DA, McShane DJ, Fries FJ, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 1988;31:315–24.
- Miyasaka N, Takeuchi T, Eguchi K. Official Japanese guideline for the use of infliximab for rheumatoid arthritis. *Mod Rheumatol* 2005;15:4–8.
- Kasukawa R, Yamadera Y, Takahashi A, Takeda I, Kanno T. Power Doppler sonography of intraarticular vascularization in knee joints of patients with rheumatoid arthritis. *Mod Rheumatol* 2004;14:149–53.
- Kasukawa R, Shio K, Kanno Y, Sato A, Takahashi A, Yamadera Y, et al. Doppler ultrasonographic characteristics of superficial and deep-flow signals in the knee joint pannus of rheumatoid arthritis patients. *Ann Rheum Dis* 2007;66:707–8.