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ORIGINAL ARTICLE

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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

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Abstract We used Doppler sonography to evaluate the therapeutic effects of infliximab on the knee and metacarpophalangeal (MCP) joints of 10 patients with rheumatoid arthritis (RA), based on the color flow signals (CFS) and resistance index (RI) of synovial vascularity. After three injections of infliximab, we observed significant improvement in numbers of tender joints ($P < 0.01$), values of C-reactive protein (CRP) ($P < 0.01$), erythrocyte sedimentation rate (ESR) ($P < 0.001$), disease activity scores including tender joints, swollen joints, and ESR (DAS28-E3) ($P < 0.0001$), and CFS of knee ($P < 0.001$) and MCP ($P < 0.05$) joints. There was no significant improvement in RI values of knee or MCP joints after the therapy. We observed significant correlation between CFS of knee joints (knee-CFS) and values of CRP ($P < 0.01$), ESR ($P < 0.01$), and DAS28-E3 ($P < 0.05$), but not between CFS of MCP joints (MCP-CFS) and values of CRP, ESR, and DAS28-E3. However, no significant correlation was observed between 10 difference values (before values–after values) of CFS grades of knee or MCP joints and 10 difference values each of CRP, ESR, or DAS28-E3. The knee joints are more suitable than MCP joints for obtaining CFS in Doppler sonography, and are more useful than MCP joints for evaluation.

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Introduction

To evaluate the therapeutic effect of tumor necrosis factor alpha (TNF-α) blockades on rheumatoid arthritis (RA), Doppler sonography of synovial vascularity has been successfully used to assess effects of infliximab[1–4] and etanercept[5–7] in patients with rheumatoid arthritis. In those studies, various joints were used as scanning sites for Doppler sonography, including the wrist,[1,6] knee,[3–5,7] metacarpophalangeal (MCP) joint,[2,5,6] and proximal interphalangeal (PIP) joint.[1,6] The selection of those joints was not based on any experimental or clinical evidence. Doppler sonographic scanning of MCP and knee joints has been performed to examine correlation between color flow signals (CFS) and resistance index (RI) of synovial vascularity in MCP and knee joints.[8] However, there have been no reports of scanning of MCP and knee joints simultaneously for evaluation of TNF-α blockades.

In the present study, we used Doppler sonography to simultaneously scan knee and MCP joints in 10 patients with rheumatoid arthritis treated with infliximab. We examined CFS and RI in the knee and MCP joints of the patients before and after the therapy, examined correlation between CFS and RI, and compared CFS and RI with values of C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and disease activity scores including tender joints, swollen joints, and ESR (DAS28-E3).

Subjects and methods

Patients

Ten patients with RA (6 women and 4 men; mean age, 57.8 years; age range, 41–74 years) were enrolled in the present

study. Mean disease duration was 8.3 years (range, 3 months to 28 years). Steinbrocher's grades were stage I in two patients, stage II in three patients, stage III in one patient, and stage IV in four patients. Methotrexate was used at 6 mg per week in eight patients and 4 mg per week in two patients. Corticosteroids (as prednisolone) were used at 6 mg/day in four patients, 5 mg/day in four patients, 10 mg/day in one patient, and 2.5 mg/day in one patient. All patients satisfied the American College of Rheumatology revised 1987 criteria for RA[9] and the official Japanese guidelines for infliximab treatment for RA.[10]

Infliximab therapy

Each patient received a total of three intravenous injections of infliximab (Remicade; Tanabe Pharmaceutical, Tokyo, Japan), on days 0, 14, and 42 at a dose of 3 mg/kg per injection. Kinds and amounts of other drugs used in each patient were not changed during these 42 days. Clinical and sonographic examinations were performed before and after the three injections of infliximab (on days 0 and 42). Clinical evaluation consisted of counting the numbers of tender joints (TJ) and swollen joints, and measuring the values of CRP and ESR. DAS28 was calculated using the numbers of TJ and swollen joints and the value of ESR (DAS28-E3).

Power Doppler sonography and spectral Doppler sonography

The methods used for power Doppler and spectral Doppler sonography are described in detail elsewhere.[3] Briefly, we used a Toshiba Aplio-80 system (Toshiba Medical Systems, Otawara, Japan) and a multidimensional linear scanner (PLT-704AT) at 5.3 MHz. Power Doppler sonography was performed using the standard method with a pulse repetition frequency of 11.7–12.2 Hz. Pulsed-wave spectral Doppler sonography was performed using a 125-Hz filter. The suprapatellar region of both knee joints and the dorsal region of the 2nd and 3rd MCP joints were scanned longitudinally and transversely. The intensity of vascularity in the joints was evaluated by counting the number of CFS, using grades established in a modification of Klauser's methods:[11,12] grade 0, no CFS; grade 1, from 1 to 4 CFS; grade 2, from 5 to 8 CFS; grade 3, more than 9 CFS. The RI of each CFS was calculated automatically using a computer, by tracing a velocity wave developed by spectral Doppler sonography using the following formula: RI = peak systolic (maximum) velocity–end diastolic (minimum) velocity/peak systolic (maximum) velocity. When CFS could not be obtained using power Doppler sonography, RI was designated as 1.0.

Mean grades of CFS and mean velocity of RI in knee and MCP joints were calculated as the mean grades of sonographic images with positive CFS or as the mean values of sonographic images with positive velocity wave, out of the total of four sonographic images (longitudinal and transverse) of each pair of knee joints and out of the total eight sonographic images (longitudinal and transverse) of the four MCP joints. A difference value was obtained by calculating the value obtained before the therapy minus the value obtained after the therapy.

Statistical analysis

Statistical analysis was performed using the J-Stat software package for Windows. Differences in values before and after infliximab therapy were evaluated using Wilcoxon signed-ranks tests. Differences in numbers of joints with CFS between knee and MCP joints were analyzed using Welch's *t*-tests. Correlation between two values was analyzed using Spearman's rank correlation coefficient. *P* values of less than 0.05 were considered to indicate significance.

Results

Clinical and Doppler sonographic findings of the 10 RA patients before and after infliximab therapy (three injections in 6 weeks) are shown in Table 1. After the therapy, the patients exhibited significant improvement in numbers of tender joints ($P = 0.0013$), and values of CRP ($P = 0.0058$), ESR ($P = 0.0003$), and DAS28-E3 ($P < 0.0001$). In the Doppler sonographic findings, numbers of joints in which CFS were obtained were significantly greater among knee joints (20/20, 100%) than among MCP joints (18/40, 45%) before the therapy ($P < 0.0001$), and were also significantly greater among knee joints (19/20, 95%) than among MCP joints (13/40, 32.5%) after the therapy ($P < 0.0001$). Consequently, the total number of CFS-positive joints before and after therapy was also significantly greater for the knee joints (39/40, 97.5%) than for the MCP joints (31/80, 38.8%) ($P < 0.0001$). There were significant improvements in mean values of CFS in knee joints (before therapy, 1.68 ± 0.67; after therapy, 1.25 ± 0.58; $P = 0.0007$) and MCP joints (before, 0.83 ± 0.61; after, 0.48 ± 0.43; $P = 0.017$) after the therapy. However, there were no significant improvements in mean values of RI in knee joints (before, 0.80 ± 0.09; after, 0.83 ± 0.11) or MCP joints (before, 0.86 ± 0.10; after, 0.89 ± 0.10).

The representative Doppler sonographic images of CFS and RI are shown in Figs. 1 and 2. The images of the left knee of patient S.M. before the therapy, exhibiting grade 2 CFS with RI of 0.76, are shown in Fig. 1a and b. The images of the left knee of patient SM after three injections of infliximab, exhibiting grade 1 CFS with RI of 0.99, are shown in Fig. 1c and d. The images of the left 3rd MCP joint of patient SM before the therapy, exhibiting grade 3 CFS with RI of 0.72, are shown in Fig. 2a and b. The images of the left 3rd MCP joint of patient SM after the therapy, exhibiting grade 1 CFS with RI of 0.82, are shown in Fig. 2c and d. We evaluated the correlation between values of CFS or RI and values of TJ, CRP, ESR, or DAS28-E3, using a total of 20 values (10 before therapy, 10 after therapy) for each variable. Numbers of TJ did not correlate with CFS in knee joints (knee-CFS), RI in knee joints (knee-RI), CFS in

Table 1. Clinical and Doppler sonographic findings of 10 patients with rheumatoid arthritis treated with three injections of infliximab

Infliximab (3 mg/kg) injection 3 times in 6 weeks	Before therapy	After therapy	*P* value
No. of tender joints (mean ± SD)	12.2 ± 6.1	3.6 ± 2.2	0.0013**
CRP (mg/dl; mean ± SD)	3.8 ± 1.8	1.3 ± 1.5	0.0058**
ESR (mm/h; mean ± SD)	79.8 ± 22.0	47.0 ± 26.4	0.0003***
DAS28-E3 (mean ± SD)	6.3 ± 0.7	4.4 ± 0.7	<0.0001****
No. of joints with color flow signals (No. examined)			
Knee (2)	20 (100%)**** |	19 (95.0%)**** |	Total 39/40 (97.5%)**** |
MCP (4)	18 (45.0%)	13 (32.5%)	Total 31/80 (38.8%)
Knee			
CFS (mean ± SD)	1.68 ± 0.67	1.25 ± 0.58	0.0007***
RI (mean ± SD)	0.80 ± 0.09	0.83 ± 0.11	0.2504 n.s.
MCP			
CFS (mean ± SD)	0.83 ± 0.61	0.48 ± 0.43	0.017*
RI (mean ± SD)	0.86 ± 0.10	0.89 ± 0.10	0.238 n.s.

CFS, color flow signals; CRP, C-reactive protein; DAS28-E3, disease activity scores including tender joints, swollen joints, and ESR; ESR, erythrocyte sedimentation rate; MCP, metacarpophalangeal (joints); RI, resistance index
* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$; **** $P < 0.0001$; n.s., not significant

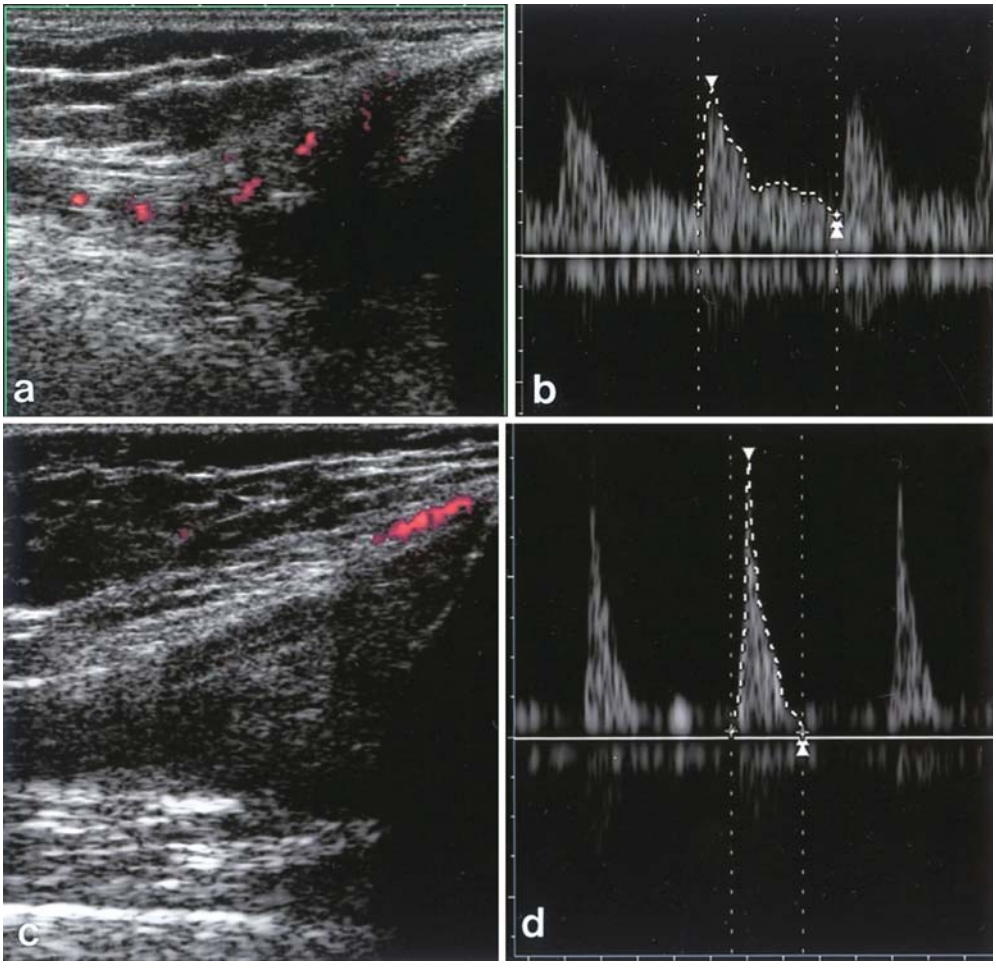

Fig. 1. Color flow signals (CFS) from longitudinal power Doppler sonography of the left knee joint of patient S.M. before (**a**) and after (**c**) three injections of infliximab, and two velocity waves of spectral Doppler sonography obtained from one of the corresponding CFS before (**b**) and after (**d**) the therapy. Grade 2 CFS (**a**) with resistance index (RI) of 0.76 (**b**) improved to grade 1 CFS (**c**) with RI of 0.99 (**d**)

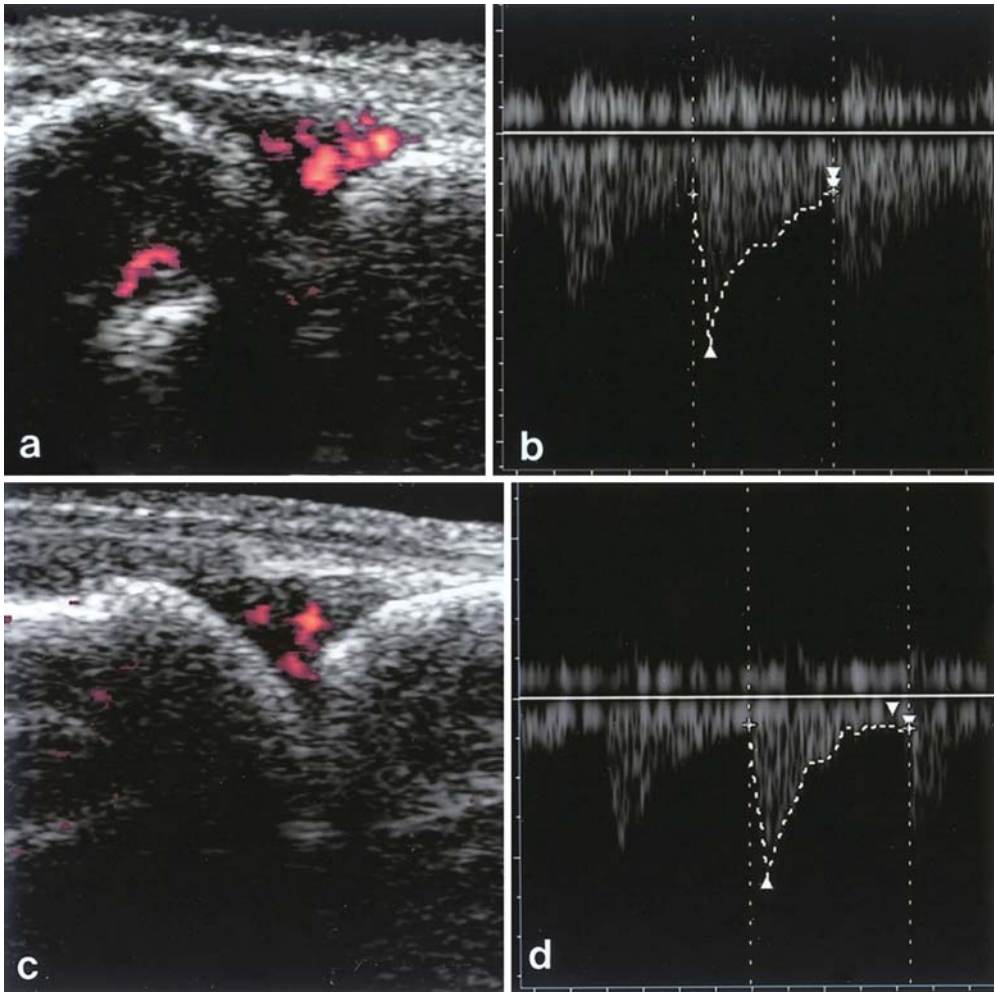

Fig. 2. Color flow signals (CFS) from longitudinal power Doppler sonography of the left 3rd metacarpophalangeal (MCP) joint of patient S.M. before (**a**) and after (**c**) three injections of infliximab, and two velocity waves of spectral Doppler sonography obtained from one of the corresponding CFS before (**b**) and after (**d**) the therapy. Grade 3 CFS (**a**) with RI of 0.72 (**b**) improved to grade 1 CFS (**c**) with RI of 0.82 (**d**)

MCP joints (MCP-CFS), or RI in MCP joints (MCP-RI). Knee-CFS correlated significantly with CRP ($r = 0.636$, $P = 0.0056$), ESR ($r = 0.600$, $P = 0.0088$), and DAS28-E3 ($r = 0.5602$, $P = 0.0146$) (Fig. 3a,c,e), whereas MCP-CFS did not significantly correlate with CRP ($P = 0.309$), ESR ($P = 0.716$), or DAS28-E3 ($P = 0.178$) (Fig. 3b,d,f). Resistance index of knee or MCP joints did not significantly correlate with CRP, ESR, or DAS28-E3 (data not shown). When we compared the difference values (before value minus after value), no significant correlations were observed between 10 CFS grades of knee or MCP joints and 10 values each of CRP, ESR or DAS28-E3 (data not shown). There was a significant correlation between CFS and RI values, in both knee ($r = –0.797$, $P = 0.0005$) and MCP joints ($r = –0.766$, $P = 0.0008$). However, there was no significant correlation between knee-CFS and MCP-CFS or between knee-RI and MCP-RI ($P = 0.410$ and $P = 0.923$, respectively).

Discussion

In the present simultaneous Doppler sonographic scanning of two knee joints and four MCP joints of 10 RA patients before and after infliximab injections, we observed a significant difference ($P < 0.0001$) in numbers of CFS between knee joints (98%, 39/40) and MCP joints (39%, 31/80). To our knowledge, this is the first report of such a significant difference in frequency of Doppler sonographic CFS between knee and MCP joints of RA patients.

After three injections of infliximab, we observed significant improvement in CFS in both knee ($P < 0.001$) and MCP ($P < 0.05$) joints of the present patients; this is similar to the findings of two previous studies in which knee joints were examined.[3,4] Similarly, significant improvements in CFS of MCP joints in infliximab therapy were observed by Ribbens et al. ($P < 0.05$)[1] at 6-week evaluation and Taylor et al. ($P < 0.05$)[2] at 18-week evaluation. In addition, in etanercept therapy, significant improvements in CFS of MCP joints were reported by Hau et al. ($P < 0.01$)[5] at 4-week evaluation and by Terslev et al. ($P < 0.01$)[6] at 2-week evaluation, and also a significant improvement in CFS of knee joints ($P < 0.001$) was reported by Fiocco et al.[7] at 12-week evaluation. However, in the present study there was no significant improvement in RI values of the knee or MCP joints, in contrast to the significant improvement in RI values of the knee joints in the above-mentioned two previous studies.[3,4] The reasons for the discrepancy between

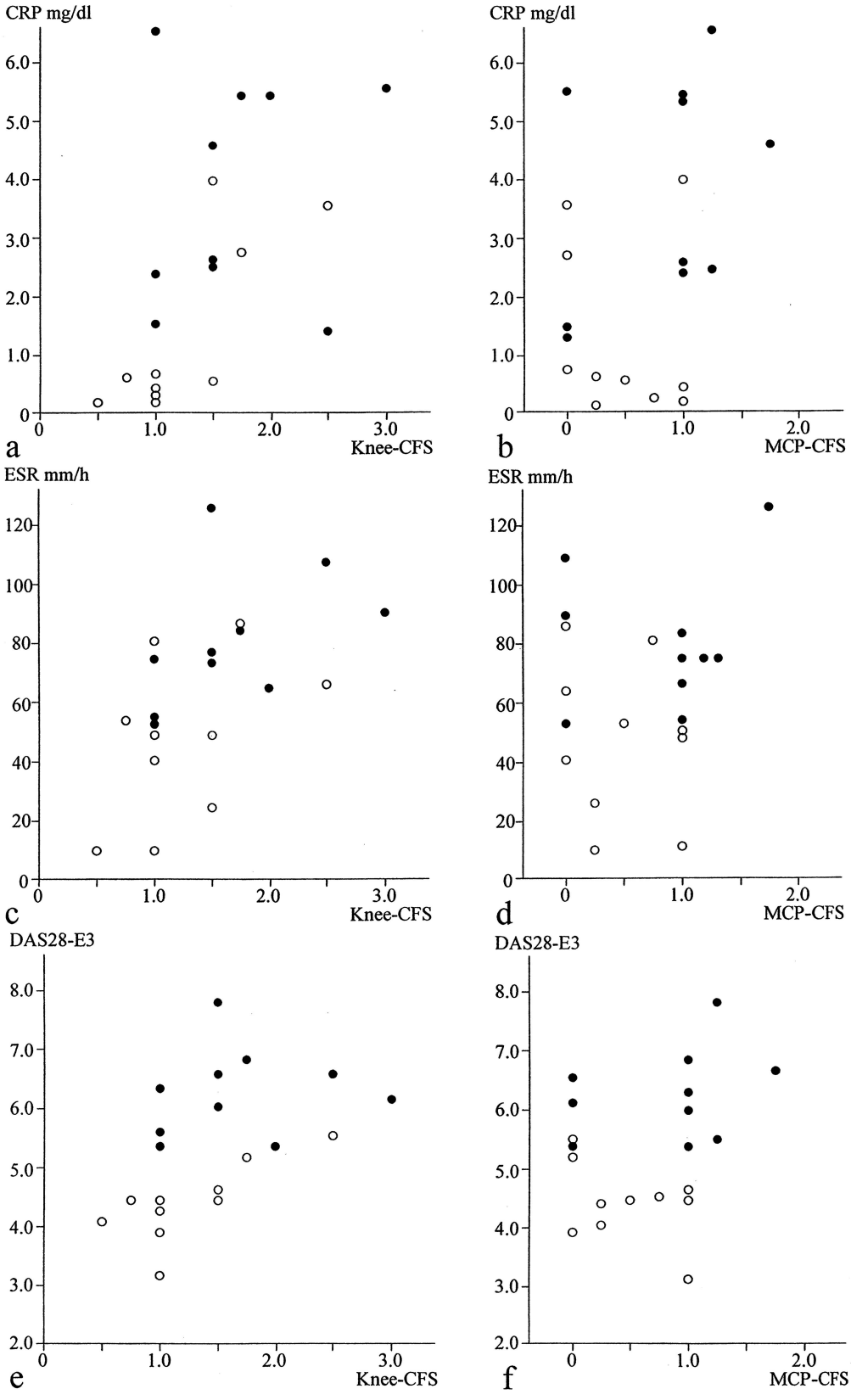

Fig. 3. Correlation between 20 (10 before: *closed circles* and 10 after: *open circles*) color flow signals (*CFS*) and 20 (10 before: *closed circles* and 10 after: *open circles*) values each of C-reactive protein (*CRP*), erythrocyte sedimentation rate (*ESR*) and disease activity score (*DAS28-E3*) in knee (**a**, **c**, **e**) and metacarpophalangeal (*MCP*) (**b**, **d**, **f**) joints. There was significant correlation between knee-CFS and values of CRP ($r = 0.636$, $P = 0.0056$) (**a**), ESR ($r = 0.600$, $P = 0.0088$) (**c**), and DAS28-E3 ($r = 0.5602$, $P = 0.0146$) (**e**). There was no significant correlation between MCP-CFS and values of CRP ($P = 0.309$) (**b**), ESR ($P = 0.716$) (**d**), or DAS28 ($P = 0.178$) (**f**). *DAS28-E3*, disease activity scores including tender joints, swollen joints, and ESR

these results are not clear. The present patients may have had more severely affected knee joints than those of the two previous studies; mean CFS for knee joints was 1.68 in the present study, compared with 1.50 and 1.54 in the two previous studies, although all three studies had the same mean RI for knee joints (0.8). The present findings that MCP-CFS did not correlate with CRP, ESR, or DAS28-E3 and that knee-CFS correlated significantly with CRP, ESR, and DAS28-E3 ($P < 0.05$, each), may be due to the lower frequency of positive CFS in MCP joints (39%), compared to knee joints (98%). The results that the difference (before–after) values did not correlate between CFS and values of CRP, ESR, and DAS28-E3 could indicate a lower association of CFS with these clinical factors. The present lower frequency of positive CFS in MCP joints (39%) may also be responsible for the lack of significant correlation between RI values of knee and MCP joints, in contrast to the significant correlation ($P < 0.01$) between knee-RI and MCP-RI observed in the previous study,[8] because a higher frequency of positive CFS in MCP joints (54%) was observed in the previous study. The present significant correlation between CFS and RI values in both knee and MCP joints is consistent with results of previous studies scanned on knee joints.[13]

In conclusion, Doppler sonographic imaging of CFS in knee and MCP joints is useful for evaluation of articular inflammation of RA patients treated with infliximab. The knee joints are more suitable than MCP joints for imaging of CFS, and are more useful for comparison of CFS with clinical and laboratory data such as CRP, ESR, and DAS28-E3 before and after therapy.

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References

1. 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 α treatment: pilot study. Radiology 2003;229:562–9.
2. 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.
3. Takahashi A, Sato A, Yamadera Y, Takeda I, Kanno T, Ohguchi Y, et al. Doppler sonographic evaluation of treatment with infliximab (Remicade) for rheumatoid arthritis. Mod Rheumatol 2005;15:37–40.
4. 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.
5. 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 α receptor (etanercept). Ann Rheum Dis 2002;61:55–8.
6. Terslev L, Torp-Pedersen S, Qvistgaard E, Kristofferssen H, Rogind H. Effect of treatment with etanercept (Enbrel, TNFR: Fc) on rheumatoid arthritis evaluated by Doppler ultrasonography. Ann Rheum Dis 2003;62:178–81.
7. 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.
8. Kasukawa R, Kanno Y, Homma F, Yamadera Y, Kanno T. Comparison in values of color flow signals and vascular resistance of synovial vascularity demonstrated by Doppler sonography between knee and metacarpophalangeal joints of patients with rheumatoid arthritis. Mod Rheumatol 2005;15:336–9.
9. Arnett FC, Edworthy SM, Bloch 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.
10. Miyasaka N, Takeuchi T, Eguchi K. Official Japanese guideline for the use of infliximab for rheumatoid arthritis. Mod Rheumatol 2005;15:4–8.
11. Klauser A, Frauscher F, Schirmer M, Halpern E, Pallwine L, Hereld M, et al. The value of contrast-enhanced color Doppler ultrasound in the detection of vascularization of finger joints in patients with rheumatoid arthritis. Arthritis Rheum 2002;46:647–53.
12. Kasukawa R, Yamadera Y, Takahashi A, Kanno T. Power Doppler sonography for detection of intraarticular vascularization in knee joints of patients with rheumatoid arthritis. Mod Rheumatol 2004;14:149–53.
13. Sato A, Takahashi A, Yamadera Y, Takeda I, Kanno T, Ohguchi Y, et al. Doppler sonographic analysis of synovial vascularization in knee joints of patients with rheumatoid arthritis: increased color flow signals and reduced vascular resistance. Mod Rheumatol 2005;15:33–6.