Mod Rheumatol (2005) 15:37–40
DOI 10.1007/s10165-004-0359-5

ORIGINAL ARTICLE

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Doppler sonographic evaluation of effect of treatment with infliximab (Remicade) for rheumatoid arthritis

Received: June 8, 2004 / Accepted: October 12, 2004

Abstract Synovial vascularization in the knee joints of six patients with rheumatoid arthritis who were treated with infliximab was evaluated by Doppler sonography. Power Doppler sonography demonstrated a significant reduction of color flow signals ($P < 0.05$), and spectral Doppler sonography demonstrated a significant increase in vascular resistance ($P < 0.05$) at week 6 (after three injections) evaluation of the therapy. A significant decrease in the number of tender joints ($P < 0.05$) and C-reactive protein value ($P < 0.05$) was also observed in these patients.

Key words Doppler sonography · Infliximab · Resistive index (RI) · Rheumatoid arthritis (RA) · Synovial vascularization

Introduction

In previous studies, power Doppler sonography has clearly demonstrated synovial vascularization in patients with rheumatoid arthritis (RA).[1–5] The therapeutic effect of disease-modifying antirheumatic drugs (DMARD) and anti-tumor necrosis factor (TNF) therapy on RA patients has usually been evaluated by clinical assessment of patients using methods such as American College of Rheumatology (ACR) core sets,[6] and by radiological evaluation of joints using methods such as the van der Heijde modification of the Sharp method.[7] Recently, the therapeutic effect of anti-TNF-α injection on RA patients has been successfully evaluated using power Doppler[8–10] and spectral Doppler sonography.[11]

In the present study, we used monoclonal antibody to TNF-α (infliximab, Remicade) to treat six patients with RA. We performed preliminary evaluation of vascularization in the knee joints using power Doppler and spectral Doppler sonography, and evaluated the clinical effect of the therapy using ACR core sets.

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Subjects and methods

Patients

Six patients with RA (5 women and 1 man; mean age, 44.2 years; age range, 29–58 years) were enrolled in the present study. Mean disease duration was 4.5 ± 2.4 years, and disease duration ranged from 2.1 to 7.5 years. All patients satisfied the ACR revised 1987 criteria for RA.[12] All patients also satisfied the indications for infliximab therapy established by three research committees of the Ministry of Health, Welfare and Labor of Japan 2003 (unpublished research report), as follows: number of tender and swollen joints ≥6; C-reactive protein (CRP) ≥2 mg/dl or erythrocyte sedimentation rate (ERS) ≥28 mm/h; low risk for optimistic infection with peripheral white blood cell count ≥4000/μl; peripheral lymphocyte count ≥1000/μl; negative test for β-D-glucan; intractable symptoms even after treatment with methotrexate (Rheumatrex) at a dose of 6 mg/week; no clearly visible lesions, or no anamnesis of tuberculosis or demyelinating lesions.

Infliximab therapy

Each patient received a total of three intravenous injections of infliximab (Remicade, Tanabe Pharmaceutical, Tokyo,

Japan) (on day 0, at week 2, and at week 6) at a dose of 3 mg/kg per injection.

Clinical and sonographic evaluation before and after three injections of infliximab (at week 6)

The patients were clinically evaluated using ACR core sets,[6] including the following factors: numbers of tender joints and swollen joints; health assessment questionnaire (HAQ); global evaluation of arthritis by patients; patient evaluation of pain; global evaluation of arthritis by physician; ESR or CRP. Improvement by 20% in the numbers of tender joints and swollen joints and three of the other five ACR core set items was evaluated as ACR 20.

Gray-scale sonography, power Doppler sonography, and spectral Doppler sonography

Gray-scale and Doppler sonography were performed using a Toshiba Aplio-80 system (Toshiba Medical Systems, Otawara, Japan). Methods for gray-scale and power Doppler sonography are described in a previous report.[5] Briefly, a multidimensional linear scanner (PLT-704AT) was used, at 11.0 MHz frequency for B-mode and at 5.3 MHz frequency for color mode. The suprapatellar region of both knees of the patients was scanned longitudinally and transversely. Intensity of synovial effusion and synovial proliferation was evaluated by gray-scale sonography using grades established by Rubaltelli et al.:[13] grade 0, thickness $<$ 1 mm; grade 1, thickness of 2–4 mm; grade 2, thickness of 5–7 mm; grade 3, thickness $>$ 8 mm. Power Doppler was performed using standard methods with a pulse repetition frequency of 11.7–12.2 kHz. The intensity of vascularization in the knee joints was evaluated by counting the number of color flow signals using grades established in a modification of Klauser's method:[5] grade 0, no color flow signal; grade 1, 1–4 color flow signals; grade 2, 5–8 color flow signals; grade 3, $>$9 color flow signals.

Pulsed-wave spectral Doppler imaging was performed using a 125-Hz filter. Spectral Doppler was performed to confirm blood flow in the areas where color flow signals were observed, and to calculate the resistance of the flow. Decreased resistance indicates an increase in perfusion of the vessels, and increased resistance indicates normalization of perfusion of the vessels. One of the color flow signals obtained by power Doppler sonography (PDS) was randomly selected, and was examined for pulse waves by spectral Doppler sonography (SDS). The marginal edge of a pulse wave in a spectral Doppler sonogram was traced with a dotted line. Then, the resistive index (RI) and pulsatility index (PI) were calculated using a computer and the following formulas: RI = peak systolic (maximum) velocity–end diastolic (minimum) velocity/peak systolic (maximum) velocity; PI = maximum velocity–minimum velocity/mean velocity. Mean grades of synovial effusion and proliferation, color signals, RI and PI of each knee joint were means of values obtained in two longitudinal or transverse scans of the knee.

Statistical analysis

Statistical analysis was performed using the Stat View J-5.0 (SAS Institute, Cary, NC, USA) software package for Apple Macintosh. Differences in values before and after the therapy were tested by Wilcoxon signed-ranks test. P values of less than 0.05 were considered to indicate significance.

Results

At week 6 (after three injections), 67% (4 of 6) of the present subjects were evaluated as ACR 20. Frequencies of sonographic improvement after the therapy in 4 ACR 20-positive and 2 ACR 20-negative patients were as follows: synovial effusion, 2/4 and 0/2; synovial proliferation, 0/4 and 0/2; color flow signals, 3/4 and 1/2; RI, 4/4 and 0/2; PI, 3/4 and 0/2, respectively. A summary of the present results is presented in Table 1. Numbers of tender joints ($P < 0.05$) and CRP values ($P < 0.05$) were significantly reduced at week 6. However, there was no significant change in grades of synovial effusion or synovial proliferation. Mean grades

Table 1. Clinical and sonographic evaluation of six patients with rheumatoid arthritis treated with infliximab

Infliximab injection	Clinical evaluation of six patients		Sonographic evaluation of twelve knee joints				
			Gray-scale		Power Doppler	Spectral Doppler	
	Mean no. of tender joints mean ± SD	Mean value of CRP mg/dl mean ± SD	Mean grade of synovial effusion mean ± SD	Mean grade of synovial proliferation mean ± SD	Mean grade of color flow-signals mean ± SD	Mean value of RI mean ± SD	Mean value of PI mean ± SD
Before	6.33 ± 1.03	3.74 ± 2.35	0.67 ± 0.65	1.00 ± 0.00	1.50 ± 0.67	0.80 ± 0.17	1.73 ± 0.65
	*	*	ns	ns	*	*	ns
After 3 injections (at week 6)	1.83 ± 0.75	0.63 ± 0.48	0.50 ± 0.52	1.08 ± 0.29	1.00 ± 0.00	0.86 ± 0.12	1.93 ± 0.54

CRP, C-reactive protein; RI, resistive index; PI, pulsatility index
*, $P < 0.05$; ns, not significant

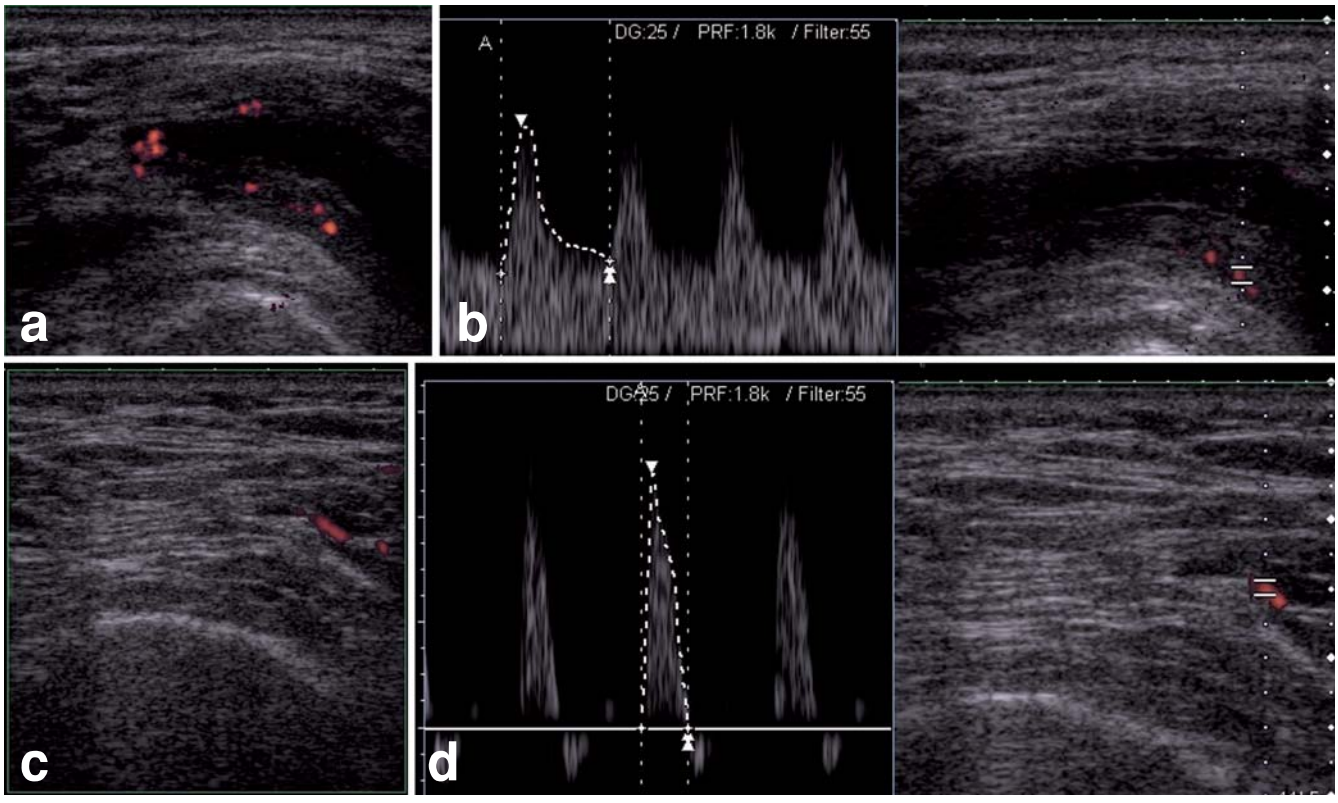

Fig. 1. Power Doppler (**a**,**c**) and spectral Doppler (**b**,**d**) sonograms obtained by transverse scan of the right knee in patient A.W., taken before (**a**,**b**) and after three injections (at week 6) (**c**,**d**) of infliximab. Color flow signals decreased from grade 3 (**a**) to grade 1 (**c**), along with a reduction of synovial effusion from grade 2 to grade 0, but synovial proliferation remained constant at grade 2. Resistive index and pulsatility index increased from 0.59 and 1.00, respectively (**b**), to 1.00 and 2.03, respectively (**d**)

of color flow signals from PDS decreased from 1.50 ± 0.67 to 1.00 ± 0.00 ($P < 0.05$). Similarly, mean RI values increased significantly from 0.80 ± 0.17 to 0.86 ± 0.12 ($P < 0.05$), indicating a reduction of vessel permeability after the treatment. However, mean PI values did not significantly increase.

Representative power Doppler and spectral Doppler sonography images (of patient A.W.) are shown in Fig. 1. Before infliximab injections, PDS of the left knee of this patient showed grade 3 color flow signals with grade 2 synovial effusion and grade 2 synovial proliferation (Fig. 1a). After three injections, PDS of the same knee showed grade 1 color flow signals with grade 0 synovial effusion and grade 2 synovial proliferation (Fig. 1c). Similarly, RI and PI values from SDS of the left knee of the same patient increased from 0.59 and 1.00, respectively (Fig. 1b), to 1.00 and 2.03, respectively (Fig. 1d), after three injections.

Discussion

Reports indicate that the intensity of vascularization in the inflammatory synovium demonstrated by PDS in RA patients correlates with intensity of articular inflammation of RA patients.[1–5] Studies suggest that decreases in RI and PI values obtained by SDS indicate increased vascular permeability.[3] This in turn suggests that increases in RI and PI indicate normalization of vascularization. To the best of our knowledge, there have been four reports about PDS evaluation of the effects of anti-TNF therapy for RA patients: two about infliximab therapy,[8,10] and two about etanercept therapy.[9,11] In a report by Ribbens et al.[8] on evaluation of infliximab therapy, the number of metacarpophalangeal (MP) joints with positive Doppler flow signals decreased from 13 joints to 5 joints at week 6, with a significant reduction of synovial thickness. In a report by Taylor et al.[10] on effects of treatment with infliximab+methotrexate (MTX) in MP joints, the area of color Doppler pixels was significantly decreased at week 18, compared with injections of placebo+MTX. In a report by Hau et al.,[9] PDS evaluation 1 month after etanercept therapy showed significant reduction of pannus vascularization. In a report by Terslev et al.,[11] PDS and SDS evaluation 2 weeks after etanercept therapy showed that the areas of the colored pixels were significantly reduced and mean RI values had recovered from reduced values to normal values. In the present study, infliximab therapy for RA patients significantly reduced the grades of color flow signals ($P < 0.05$) on PDS and significantly increased RI values ($P < 0.05$) on SDS in the knee joints, but not grades of synovial effusion and synovial proliferation, along with significant improvement in num-

bers of tender joints ($P < 0.05$) and CRP values ($P < 0.05$). Metacarpophalangeal joints examined by other investigators are obviously more suitable for evaluation of the intensity of arthritis in RA patients than knee joints examined by us. However, the sonography of MP joints is technically difficult to test and to evaluate the results, to which we are not trained enough at present. In the previous study on intra-articular vascularization by power Dopplex sonography,[5] we demonstrated that the intensity of the color flow signals in the knee joints of RA patients correlated significantly with CRP values ($P < 0.05$) of the patients. Therefore, we considered that knee joint sonography could indicate the inflammatory grade of arthritis in RA patients, although that was no better than MP joint sonography. It has been reported that anti-TNF antibody affects TNF-induced release of nitrogen oxide from endothelial cells, causing a reduction of vascularization.[10] Because the effects of infliximab therapy appear rapidly after injection, quick methods for evaluation of its therapeutic effects are required. Power Doppler and spectral Doppler technique are more suitable for evaluation of synovial vascularization in the joints than other imaging techniques such as radiography, scintigraphy, computed tomography, or magnetic resonance imaging.

In conclusion, we found that power Doppler and spectral Doppler sonography can clearly visualize synovial vascularization and vascular resistance. Our preliminary findings indicate that Doppler sonography is useful for evaluation of the therapeutic response of RA patients to infliximab treatment.

Acknowledgment We express our sincere thanks to Mr. K. Nihei of the Library Unit of Ohta Nishinouchi Hospital for his technical help in making sonographic photographs.

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