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ORIGINAL ARTICLE

Radiographic progression in weight-bearing joints of patients with rheumatoid arthritis after TNF-blocking therapies

Eiko Seki · Isao Matsushita · Eiji Sugiyama · Hirohumi Taki · Koichiro Shinoda · Hiroyuki Hounoki · Hiraku Motomura · Tomoatsu Kimura

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Abstract The aim of the present study was to assess the influence of tumor necrosis factor (TNF)-blocking therapies on weight-bearing joints in patients with rheumatoid arthritis. Changes in clinical variables and radiological findings in 213 weight-bearing joints (69 hip joints, 63 knee joints, and 81 ankle joints) of 42 consecutive patients were investigated at baseline and at 1 year of TNF-blocking therapies. Structural damage to the weight-bearing joints was assessed using the Larsen scoring method. Detailed comparisons of the sizes and locations of erosions were performed for each set of radiographs of the respective joints. Assessment of radiographs of the 213 weight-bearing joints indicated progression of the Larsen grade in eight joints. Another five joints without Larsen grade progression showed apparent radiographic progression of joint damage based on increases in bony erosions. Overall, 13 joints (6%) of eight patients (19%) showed progression of joint damage after 1 year of TNF-blocking therapies. Analysis of each baseline grade indicated that radiographic progression of joint damage was inhibited in most grade 0–II joints. On the other hand, all hip and knee joints with pre-existing damage of grade III/IV showed apparent progression even in patients with good response. The results further suggested that radiographic progression may occur in less damaged joints when the patients were non-responders to the therapy. Among the weight-bearing joints, ankle joints showed different radiographic behavior and four ankle joints displayed improvement of radiographic damage. Early initiation of anti-TNF therapy should be necessary especially when the patients are starting to show early structural damage in weight-bearing joints.

Keywords Anti-TNF therapy · Etanercept · Infliximab · Radiographic progression · Rheumatoid arthritis · Weight-bearing joint

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease that causes joint pain, swelling, and stiffness, leading to structural damage. Joint damage appears early in the disease course, shows continuous progression, and accounts for a substantial proportion of disability in RA [1]. Although the etiology of RA remains to be clarified, it is already well known that tumor necrosis factor (TNF) α is among the most important inflammatory cytokines for treatment of RA. Therapies involving biological antibodies against TNFα or soluble TNFα receptor have been shown to remarkably reduce the associated inflammation and inhibit the progression of joint damage [2, 3]. The dramatic reduction in joint damage by TNF-blocking therapies sometimes includes 'repair' of joint erosion and radiographic inhibition, even in patients who have residual joint

E. Seki (✉) · I. Matsushita · H. Motomura · T. Kimura
Department of Orthopaedic Surgery, Faculty of Medicine, University of Toyama,
2630 Sugitani,
Toyama, Toyama 930-0194, Japan
e-mail: eikok@med.u-toyama.ac.jp

E. Sugiyama · H. Taki · K. Shinoda · H. Hounoki
First Department of Internal Medicine, Faculty of Medicine, University of Toyama,
Toyama, Japan

inflammation [4, 5]. Thus, radiographic progression has attracted much attention and became a major outcome variable of RA. However, the assessment of joint damage is mainly restricted to small joints in the hands and feet. Since radiographic damage of large weight-bearing joints, such as the hips, knees, and ankles, is strongly associated with walking disability and an important determinant of functional capacity in patients with RA [6, 7], it is indispensable to assess the extent of radiographic damage in these joints after TNF-blocking therapies.

The purpose of the present study was to assess the influence of TNF-blocking therapies on large weight-bearing joints in patients with RA after 1 year. The following three aspects were addressed: (a) whether there was inhibition or progression of large joint damage; (b) whether there was progression of joint damage related to the baseline damage; and (c) whether there was possible repair in large joints.

Materials and methods

Patients and therapies

All patients fulfilled the American College of Rheumatology 1987 revised criteria [8] for a diagnosis of RA. The TNF-blocking therapy was in accordance with the Japan College of Rheumatology Guidelines [9, 10]. Inclusion criteria were active RA with ≥6 swollen, ≥6 tender joints, C-reactive protein (CRP) of ≥2.0 mg/dl, and an erythrocyte sedimentation rate (ESR) of ≥28 mm/h. All patients had an inadequate response to one or more recommendation level A disease-modifying antirheumatic drugs (DMARDs). The patients were also required to have white blood cell counts of $\geq 4{,}000/\text{mm}^3$ and peripheral blood lymphocyte counts of $\geq 1{,}000/\text{mm}^3$ in addition to negative β-D-glucan in sera in order to avoid possible opportunistic infections, including tuberculosis and *Pneumocystis jiroveci* pneumonia. The patients were treated with methotrexate (MTX) and infliximab at a standard dosage of 3 mg/kg intravenously at 0, 2, and 6 weeks, and every 8 weeks thereafter, or with etanercept at a dose of 25 mg once or twice weekly by subcutaneous injection.

Radiographic assessment

Standard anteroposterior radiographs of all weight-bearing joints (hips, knees, and ankles), irrespective of the clinical symptoms, were taken at baseline and at 1 year of the therapy. Joints that had already received total joint arthroplasty or arthrodesis before the initiation of TNF-blocking therapies were excluded from the radiographic analysis. Structural damage to the hip, knee, and ankle joints was assessed by two observers (I.M. and E.S.) according to Larsen et al. [11] using standard reference films, and in cases of disagreement, a consensus was reached by the observers. The method of Larsen et al. has reasonable sensitivity, satisfactory intra- and inter-observer reliability [12, 13], and the six grades of the Larsen classification are as follows: grade 0 (no change), the normal status of the joint; grade I (slight changes), periarticular soft tissue swelling, osteoporosis, and slight joint space narrowing; grade II (definite early changes), erosion and joint space narrowing correspond to the standards, erosion is obligatory except in the weight-bearing joints; grade III (medium destructive changes), erosion and joint space narrowing correspond to the standards, erosion is obligatory in all joints; grade IV (severe destructive changes), erosion and joint space narrowing correspond to the standards, bone deformation is present in the weight-bearing-joints; and grade V (mutilating changes), the original articular surfaces have disappeared, gross bone deformation is present.

In addition to the Larsen grade for large joint evaluation, changes in sizes and locations of erosions were compared in detail for each set of radiographs from each patient as previously described [14, 15]. Joint damage was assessed by a combination of progression of the Larsen grade and progression of bony erosions.

Disease activity and clinical response

Routine laboratory tests, including ESR, CRP, and matrix metalloproteinase-3 (MMP-3), were performed for each patient at baseline and at regular intervals thereafter. As a parameter of disease activity, the 28-joint Disease Activity Score (DAS28-CRP) [16, 17] was used. Clinical response at 1 year was defined according to the European League Against Rheumatism (EULAR) response criteria based on the DAS28 [18]. Body mass index (BMI) that may influence joint damage [19, 20] was also measured at baseline.

Statistical analysis

The frequencies of progression of joint damage in each of weight bearing joints were compared between joints of Larsen grades 0–II and joints of Larsen grades III–V, using Fisher's exact testing. The baseline disease characteristics (baseline CRP, ESR, MMP-3, and BMI) of patients with or without progression of joint damage were compared using the Mann–Whitney test. Values of $p<0.05$ were considered to indicate statistical significance. If patients had discontinued treatment before 1 year, last observation carried forward approach was used to account for missing date at 1 year in estimation of radiographic progression and disease activity.

Results

Baseline characteristics of the patients and joints

A total of 42 patients, comprising six men and 36 women, were enrolled in this study (Table 1). The median age of the patients was 58 years, and the median duration of RA was 9 years. Most patients (93%) received MTX before TNF-blocking therapies either as monotherapy or in combination with different DMARDs. Furthermore, 33 patients (79%) received corticosteroids, with median dose of 4 (interquartile range, 2–7) mg/day. The patients had moderate to high levels of disease activity. Infliximab and etanercept were used in 29 and 13 patients (including four cases that switched from infliximab), respectively. Five patients withdrew for lack of efficacy at 6, 8, 8, 10, and 11 months. A total of 213 weight-bearing joints (69 hips, 63 knees, and 81 ankles, excluding joints with preceding surgery) were analyzed for their baseline Larsen grades (Table 2): grade 0, 52 joints (24%); grade I, 124 joints (58%); grade II, 15 joints (7%); grade III, 12 joints (6%); grade IV, ten joints (5%); grade V, zero joints (0%).

Progression of joint damage

Assessment of radiographs of the 213 large weight-bearing joints indicated Larsen grade progression in eight joints (five joints from grades I to II, and three joints from grades III to IV). Another five weight-bearing joints that remained at the same Larsen grade showed apparent progression of joint damage based on remarkable increases in bony

Table 1 Baseline characteristics of the patients (n=42)

Demographics	Values
Age, median (range) (years)	58 (42–75)
Men/women	6/36
Disease characteristics	
Disease duration, median (range) (years)	9 (0.5–45)
CRP (mg/dl)	3.5 (2.4–5.4)
ESR (mm/1st h)	81 (58–98)
MMP-3 (ng/ml)	266 (153–453)
DAS28-CRP	4.9 (4.4–5.6)
Concomitant treatment	
Concomitant methotrexate, n (%)	39 (93)
Methotrexate dose (mg/week)	8 (6–8)
Concomitant corticosteroids, n (%)	33 (79)
Corticosteroid dose (mg/day)	4 (2–7)

Except where indicated otherwise, values are the median (interquartile range)

CRP C-reactive protein, *ESR* erythrocyte sedimentation rate, *MMP-3* matrix metalloproteinase-3, *DAS28* Disease Activity Score 28–joint assessment

Table 2 Baseline characteristics of the joints

Larsen classification	Total (n=213)	Hips (n=69)	Knees (n=63)	Ankles (n=81)
Grade 0	52	21	8	23
Grade I	124	43	45	36
Grade II	15	3	5	7
Grade III	12	1	3	8
Grade IV	10	1	2	7
Grade V	0	0	0	0

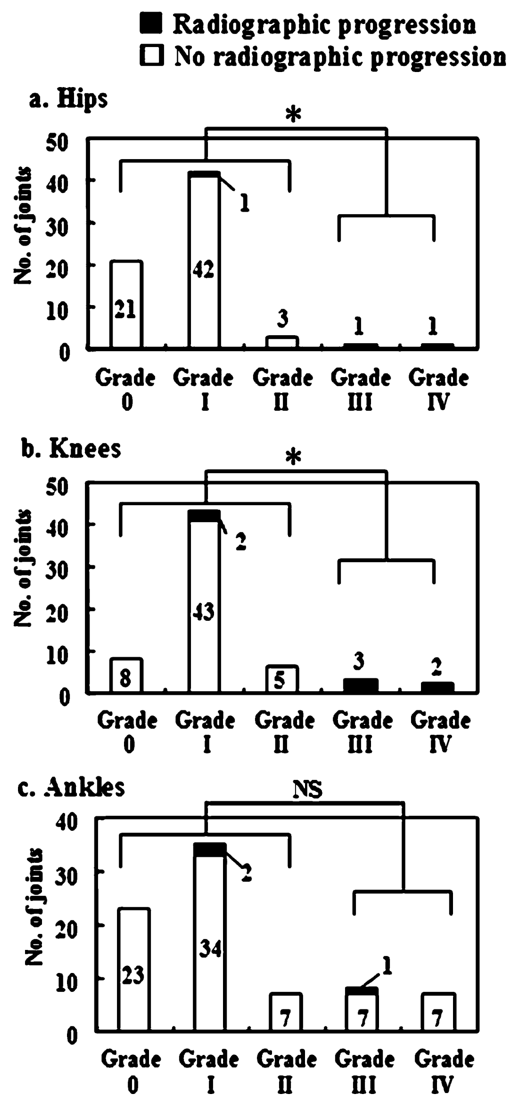

Fig. 1 Baseline Larsen grades and radiographic progression. Radiographic progression in hip (**a**) and knee (**b**) joints is practically inhibited in grade 0–II joints, whereas joints with pre-existing damage of Larsen grade III or IV are highly disposed to progression (*p<0.05, grade 0–II joints vs. grades III and IV joints). On the other hand, ankle joints (**c**) show somewhat different radiographic behavior (*NS* not significant, p=0.96). Most of the ankle joints do not show progression of joint damage, irrespective of the degree of pre-existing damage

erosions. Overall, 13 joints (6%) of eight patients (19%) showed progression of joint damage after 1 year of TNF-blocking therapies. Analysis according to the baseline grade of each hip, knee, and ankle joint indicated progression of hip joint damage in only one of 67 joints of Larsen grades 0–II, whereas both of two hip joints of Larsen grades III and IV showed radiographic progression (Figs. 1a and 2a). Similarly, only two knee joints of Larsen grades 0–II showed progression of joint damage, whereas all knees of Larsen grades III and IV exhibited apparent progression (Figs. 1b and 2b). Statistical analysis showed significant difference in frequency of progression of hip and knee joint damage between joints of Larsen grades 0–II and joints of Larsen grades III and IV ($p<0.05$). Thus, radiographic progression of hip and knee joint damage is practically inhibited in grades 0–II joints, whereas joints with pre-

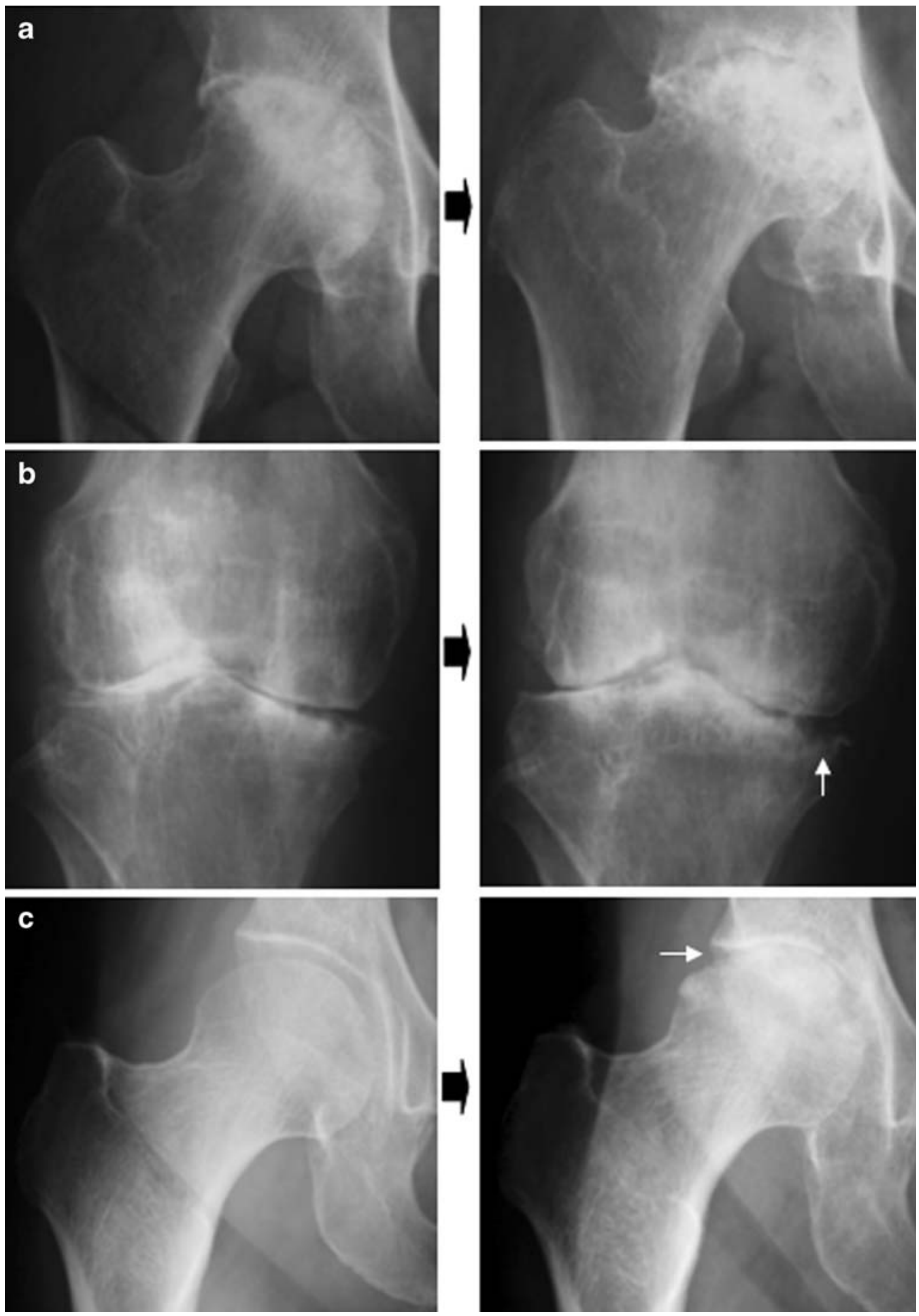

Fig. 2 Progression of joint destruction. **a** Grade III hip joint of 63-year-old woman progressed to grade IV during 1 year of TNF-blocking therapy, although the patient showed a good response. **b** Knee joint of 58-year-old woman remained at Larsen grade IV after 1 year TNF-blocking therapy, but the progression of erosion was apparent (*small arrow*). **c** Less damaged grade I hip joint of 64-year-old woman with no response to TNF-blocking therapy progressed to grade II damage and loss of joint space (*arrow*)

existing damage of Larsen grade III or greater are highly disposed to progression despite TNF-blocking therapies.

On the other hand, among the weight-bearing joints, the ankle joints showed somewhat different radiographic behavior (Fig. 1c). Most of the ankle joints did not show progression of joint damage, irrespective of the degree of pre-existing damage. Statistical analysis showed no significant difference in frequency of progression of ankle joint damage between joints of Larsen grades 0–II and joints of Larsen grades III and IV (p=0.96). Furthermore, detailed evaluation of each set of radiographs suggested improvement of the damage in four ankle joints: one joint of grade III and three joints of grade IV. Representative cases with such healing phenomenon including improvement of erosion and subchondral structure in ankle joints are shown in Fig. 3.

Disease activity and radiographic progression

We compared the baseline characteristics of the CRP, ESR, MMP-3, and BMI levels of the patients with and without radiographic progression in weight-bearing joints (Fig. 4). A higher CRP level at baseline was significantly correlated with progression of joint damage (p<0.05). This correlation was apparent in joints with lower Larsen grades. Higher MMP-3 level at baseline was significantly correlated with progression of joint damage in joints with higher Larsen grades (p<0.05), whereas no such correlations were observed for the ESR levels. BMI, which may be one of the factors affecting joint deterioration, was not correlated with the radiographic progression at 1 year.

A total of 13 joints that showed radiographic progression were evaluated by clinical response at 1 year using the EULAR response criteria (Fig. 5). The results suggested that, even in patients with good responses, damaged weight-bearing joints of Larsen grades III and IV showed progression. The results further suggested that radiographic progression may occur in less-damaged joints (grade I) when the patients were non-responders to the TNF-blocking therapies (Fig. 2c). Statistical analysis showed significant difference in frequency of less-damaged grade I joint that resulted in radiographic progression between no response and moderate–good response (p<0.05).

Taken together, the present results indicate that radiographic progression in most weight-bearing joints is inhibited by TNF-blocking therapies. However, joints with

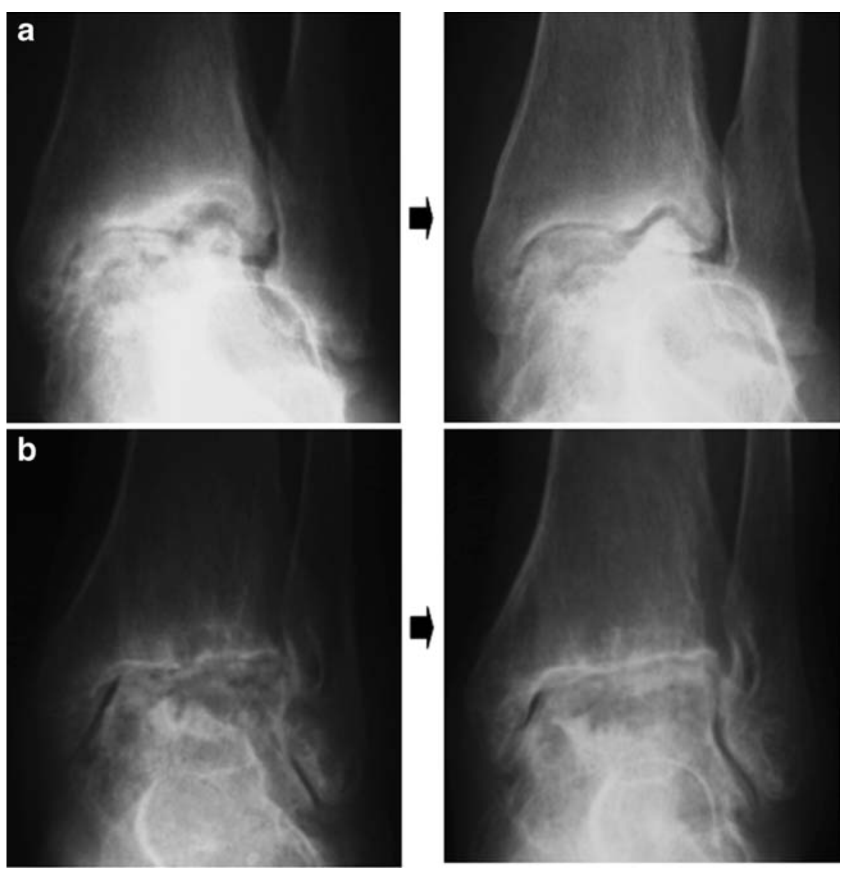

Fig. 3 Repair of erosion observed in ankle joint. **a** Ankle joint of 42-year-old woman showed Larsen grade IV damage, joint space narrowing, and severe erosion in the tibia at baseline. After 1 year of TNF-blocking therapy, repair of the erosion and partial restoration of the joint space were evident. **b** Ankle joint of 69-year-old woman showing improvement of erosion and subchondral bone structure after 1 year of TNF-blocking therapy

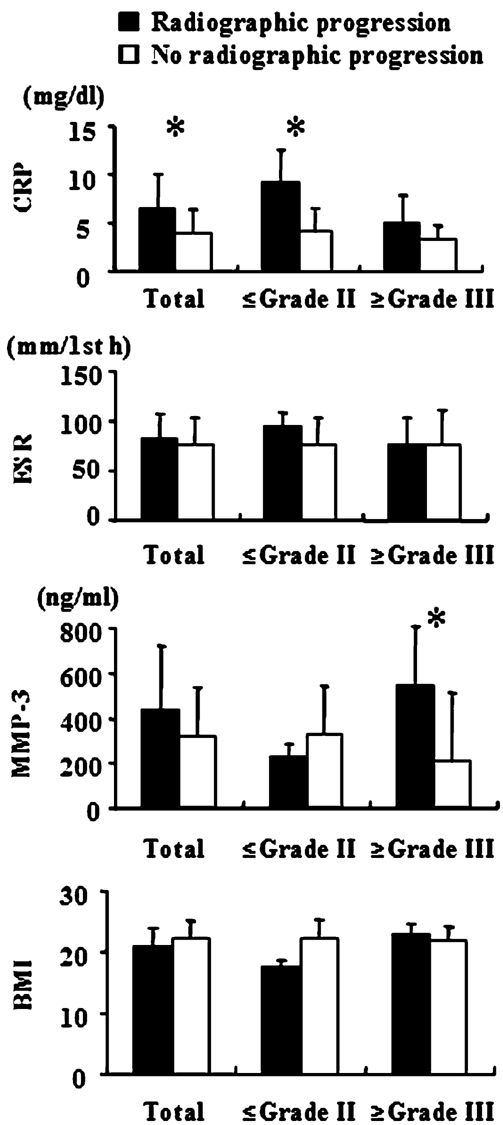

Fig. 4 Baseline characteristics and radiographic progression in weight-bearing joints. A higher CRP level at baseline is significantly correlated with progression of joint damage (*$p<0.05$). Higher MMP-3 level at baseline was significantly correlated with progression of joint damage in joints with higher Larsen grades (*$p<0.05$)

pre-existing damage of Larsen grade III or greater, especially hips and knees, show progression. Ankle joints behave differently and may show radiographic repair.

Discussion

Although progressive joint destruction is a hallmark of RA, recent studies have demonstrated the effectiveness of TNF-blocking therapies for inhibition of radiographic progression, regardless of the baseline disease activity or joint damage [2–4, 21, 22]. However, the effects on the large weight-bearing joints, which are the major determinants of RA-related disability during activities such as standing, walking, and transferring weight, have not been clarified. Previous reports have already indicated that most of the patients (64 to 93%) receiving TNF-blocking therapies (infliximab, etanercept, or adalimumab) demonstrated no radiographic progression (change in total Sharp score ≦ 0.5 from baseline) at 1 year, and such effect was higher in combination therapy with MTX [2, 21–23]. In the present study, we have observed similar therapeutic effect on the weight-bearing joint, namely, 94% of the joints and 81% of the patients showed no apparent radiographic progression at 1 year. However, analysis of individual joints indicated that all of the hip and knee joints with moderate to advanced pre-existing damage resulted in radiographic progression even after TNF-blocking therapies. Such progression could also occur among less damaged joints when the patients were non-responders to the TNF-blocking therapies.

It is obvious that mechanical factors affect the integrity of articular structures, and overloading is a potential risk factor for joint destruction in various conditions [24]. In addition, excessive weight-bearing during exercise has been reported to cause radiographic damage progression in large joints of patients with RA, and joints with pre-existing extensive damage are more susceptible to this progression [25]. Thus, loading or weight-bearing plays an important role during the progression of joint damage in RA. The present observation suggested that joints with apparent structural damage were vulnerable to further radiographic progression. In such joints, the inhibitory effect of the TNF blockade seemed to be overwhelmed by the weight-bearing status. These results appear to support the importance, indeed requirement, for early anti-TNF therapy to inhibit the progression of joint damage before the patients start to show early radiographic damage in weight-bearing joints.

The radiographic progression in another weight-bearing joint, the ankle joint, was somewhat different from that

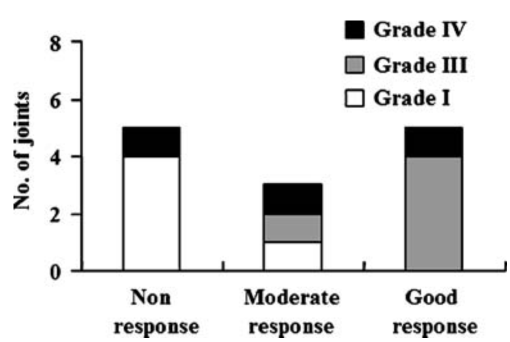

Fig. 5 EULAR response criteria at 1 year and joints that showed radiographic progression. Even in patients with a good response, weight-bearing joints with pre-existing damage of Larsen grades III and IV show progression

observed in hip and knee joints. In fact, several patients showed improvement of erosion of the ankle joints in the present study. It remains unclear whether or how TNF blockers affect ankle joint damage and healing. However, ankle joints may behave differently after therapeutic interventions, such as synovectomy. Radiographic progression is known to continue after synovectomy of the knee or other joints in many cases. On the other hand, ankle synovectomy may inhibit joint destruction in a certain population of patients with RA and lead to an increased joint space [26, 27]. Healing of joint damage, if any, could be defined as follows: (1) reappearance (and sclerosis) of the cortical plate, (2) partial or complete filling in of an erosion, or (3) subchondral bone sclerosis with osteophyte formation (secondary osteoarthritis) [14]. Although care should be taken when interpreting radiographic changes or improvement, we believe that there is a high possibility that TNF-blocking therapies inhibit the progression of ankle joint deterioration, regardless of the grade of baseline joint damage.

The present study has a limitation in determining the strength of protective effect of TNF-blocking therapies on the weight-bearing joints, since the study does not analyze the radiographic changes in patients without TNF-blocking therapies. Nevertheless, the information should be useful for understanding the effect and limits of anti-TNF therapies on the weight-bearing joints with different degree of baseline radiographic damage.

In summary, our results show that the progression of joint damage was mostly inhibited in weight-bearing joints as well as in small joints, while damaged weight-bearing joints of Larsen grades III and IV at baseline showed progression even in patients with a good response. These findings appear to support the importance of the early initiation of anti-TNF therapy for RA patients before or at the appearance of minor radiographic changes in the weight-bearing joint.

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Disclosures None

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