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ORIGINAL ARTICLE

# BIOLOGIC THERAPY SUPPRESSES SUBCLINICAL INFLAMMATION IDENTIFIED BY MAGNETIC RESONANCE IMAGING IN RHEUMATOID ARTHRITIS PATIENTS IN CLINICAL REMISSION STATE.

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**Abstract** Subclinical inflammation and radiographic progression have been described in rheumatoid arthritis patients in clinical remission state. The aim of this study was to compare the effect of biologics and nonbiologics treatment for reduction of subclinical inflammation estimated by magnetic resonance imaging (MRI). Clinical remission was judged according to the Disease Activity Score (DAS) 28-ESR. Dominant hand and wrist was evaluated using a conventional 1.5 or 3T MRI scanner. Synovitis, erosions and bone marrow edema were scored according to the Simplified Rheumatoid Arthritis MR Imaging Score (SAMIS). Twenty four patients who had reached to clinical remission with biologics (n=14) or nonbiologics (n=10) were included in the study. There were no significant differences in DAS28-ESR, Simplified Disease activity Index (SDAI), and Matrix Metalloproteinase (MMP) -3 between the biologics group and the nonbiologics group at clinical remission. However, SAMIS and bone edema score in the biologics group were significantly lower than that in the nonbiologics group. Our results suggested that biologics treatment might be superior to nonbiologics treatment to suppress bone edema and to regulate subclinical inflammation.

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**Key words:** Rheumatoid arthritis; MRI; clinical remission; subclinical inflammation; bone marrow edema.

原　著

# 関節リウマチ患者に対する生物学的製剤による治療は臨床的寛解時における MRI で検出される潜在的関節炎を抑制する

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**抄録**　関節リウマチ(RA)の治療進歩により多くの症例で臨床的寛解が得られるようになったが，一方で臨床的寛解が維持されていても関節破壊が進行する症例が存在する．そういった潜在的関節炎の制御が画像的寛解であり，関節破壊の進行抑制のための治療目標になると考えられる．

生物学的製剤(14例)あるいは非生物学的製剤(10例)にて治療を行い臨床的寛解が得られ，治療の前後で MRI にて評価を行った RA 患者24例に関して，その治療効果について解析を行った．臨床的寛解は DAS28-ESR < 2.6とし，MRI の評価は，SAMIS(Cyteval et al., Radiology 2010)を用い erosion，synovitis，bone edema について解析した．臨床的寛解時，生物学的製剤治療群は，SAMIS 4.6 (synovitis; 1.3, erosion; 2.9, bone edema; 0.5)であった．一方，非生物学的製剤群では，SAMIS 10.5 (synovitis; 2.7, erosion; 6.1, bone edema; 1.7)であった．

臨床的寛解時，非生物学的製剤群に比べ生物学的製剤投与群の SAMIS, bone edema score 値は有意に低値であった．生物学的製剤治療における MRI 画像所見での骨髄浮腫抑制効果及び潜在的関節炎の制御効果が示唆された．

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## Introduction

For patients with rheumatoid arthritis (RA), therapeutic objective is inhibition of radiographic structural progression[1, 2]. Clinical remission has been an achievable therapeutic goal in the past decades, however, recent studies showed that radiographic progression might occur in case who maintained clinical remission[3, 4]. This indicates that subclinical residual inflammation might be present in RA patients if they would reach clinical remission. MRI provides the potential to improve the evaluation of disease activity beyond clinical findings. Recent studies have demonstrated that subclinical residual inflammation identified by MRI may be present in RA patients with clinical remission or low disease activity[5, 6] and be related to subsequent radiographic progression.

The objective of this study was to clarify the efficacy of biologic therapy for regulation of subclinical inflammation. We compared clinical and laboratory data and MRI findings retrospectively in RA patients with clinical remission between biologic therapy and nonbiologic therapy.

## Patients and Methods

Patients. To be included in the study, patients had to have established RA, which was defined according to the American College of Rheumatology (ACR) 1987 criteria[7] from April 2008 to September 2011. Patients in clinical remission defined as disease activity score 28-ESR (DAS28-ESR) < 2.6 with MRI data were included. Patients were treated by disease-modifying antirheumatic drugs (nonbiologic group) or biologics with or without DMARDs (biologic group). The treatment was based on 2008 ACR recommendations. In patients with contraindication to methotrexate (MTX), they were treated by an anti-Tumor Necrosis Factor α (TNFα) agent or other combinations of DMARDs. In patients unable to take an anti-TNFα agent due to hepatitis B, latent tuberculosis infection and economical limitations, DMARDs were selected. In both groups, MRI of hands was performed at the baseline and at least 2 months after clinical remission. Clinical data (age, sex, disease duration, treatment, tender joint count, and swollen joint count) and laboratory tests (MMP-3 and anti-cyclic citrullinated peptide antibody status) were collected at the baseline and clinical remission. DAS28-ESR and the Simplified Disease activity Index (SDAI) proportions of patients in clinical remission (DAS28-ESR < 2.6, SDAI < 3.3) for different composite indices were calculated.

Imaging evaluation of MRI. The dominant hand and wrist was evaluated by a conventional 1.5 or 3T MRI scanner. Synovitis, erosions and bone marrow edema were scored according to the Simplified Rheumatoid Arthritis MR Imaging Score (SAMIS) [8] by an independent, trained rheumatologist. Briefly, the following 15 areas were evaluated for bone edema and erosion: metacarpal head and phalangeal base of the second to the fifth metacarpophalangeal joints, first metacarpal base, trapezium, scaphoid, lunate, and distal end of the lunate and radius. Both intracarpal and radiocarpal joints were combined for synovitis scoring. Erosions were scored with a scale from 1 to 10. Bone edema and synovitis were respectively scored with a scale from 0 to 1 and 0 to 2.

Statistical analysis. Data evaluation and statistical analysis were performed using GraphPad Prism version 5 software (MDF). Normally distributed continuous data were analyzed using parametric tests (independent t-test) and were summarized with means and standard deviations. Non-normally distributed continuous data were analyzed using nonparametric tests (Mann-Whitney U test) and were summarized with means and standard deviations. A value of $P < 0.05$ was considered to

**Table 1** Patients' demographics in this study.

| Patient No. | Age (year) | Sex | Disease Duration (month) | Stage | Class | Biologics | MTX (mg/week) | FK506 (mg/day) | PSL (mg/day) | Other DMARDs |
|---|---|---|---|---|---|---|---|---|---|---|
| Biologics group | | | | | | | | | | |
| 1 | 36 | M | 24 | I | 1 | IFX | 6 | − | − | |
| 2 | 66 | F | 49 | II | 1 | TCZ | 3 | − | − | |
| 3 | 49 | F | 120 | II | 1 | IFX | 6 | − | − | SASP |
| 4 | 79 | M | 34 | I | 2 | ETN | − | − | − | |
| 5 | 33 | M | 32 | III | 1 | ETN | 8 | − | − | BUC |
| 6 | 36 | F | 36 | I | 1 | ETN | − | − | − | |
| 7 | 76 | F | 36 | II | 1 | ETN | 4 | − | − | SASP |
| 8 | 52 | M | 34 | I | 1 | ADA | 6 | − | − | |
| 9 | 67 | F | 144 | II | 1 | ADA | 4 | − | − | |
| 10 | 25 | M | 28 | I | 1 | TCZ | 8 | − | − | |
| 11 | 68 | F | 144 | III | 1 | ADA | − | − | − | |
| 12 | 69 | F | 48 | II | 1 | ETN | 8 | − | − | |
| 13 | 51 | F | 120 | III | 1 | ETN | 6 | − | − | |
| 14 | 62 | M | 24 | I | 1 | ETN | 5 | − | − | SASP |
| Non-biologics group | | | | | | | | | | |
| 1 | 73 | M | 38 | II | 1 | − | 6 | 2 | − | |
| 2 | 37 | F | 41 | II | 1 | − | 6 | 3 | − | |
| 3 | 60 | M | 36 | II | 1 | − | − | 3 | − | |
| 4 | 62 | M | 36 | II | 1 | − | 12.5 | − | 5 | SASP |
| 5 | 66 | M | 36 | III | 1 | − | − | 2 | − | |
| 6 | 59 | F | 24 | I | 1 | − | 6 | 3 | − | |
| 7 | 57 | M | 40 | I | 1 | − | − | 2.5 | − | |
| 8 | 74 | M | 36 | I | 1 | − | − | 1.5 | − | |
| 9 | 45 | F | 12 | I | 1 | − | 10 | − | 5 | |
| 10 | 61 | F | 24 | I | 1 | − | − | 3 | 2.5 | |

Stage was determined according to the Steinblocker's classification, and class was determined according to the Hochberg's classification. F: female; M: male; MTX: methotrexate; PSL: prednisolone; DMARDs; disease modifying anti rheumatic drugs; SASP: salazosulfapyridine; BUC: bucillamine; IFX: infliximab; TCZ: tocilizumab; ETN: etanercept; ADA: adalimumab.

be significant.

## Results

Patients' characteristics at baseline or clinical remission. We included 24 patients in the study. The patients' characteristic data obtained at baseline are shown in Table 1. In the biologics group, two patients were treated with infliximab (IFX), seven with etanercept (ETN), three with adalimumab (ADA) and two with tocilizumab (TCZ). In nonbiologics group, five patients were receiving taclorimus (FK506), two patients were receiving MTX, and three patients were receiving both MTX and FK506.

The clinical and laboratory characteristics of patients with RA at baseline and clinical remission were indicated in table 2. The biologics group was predominantly female (57.1%) with a mean age of 55.0 years. Sixty-four percent of the patients were anti-CCP antibody positive and the mean disease duration was 62.3 months. The nonbiologics group was predominantly male (female: 40.0%) with a mean age of 60.0 years. Ninety percent of the patients were anti-CCP antibody positive and the mean disease duration was 32.3 months. In the biologics group, DAS28-ESR decreased from 5.3±1.0 (mean±SD) at base line to 1.5±0.7 at clinical remission. SDAI and MMP-3 also decreased from 24.8±11.7 (mean±SD) and 193.0±175.0 at base line to 1.2±1.2 and 56.6±24.5 respectively at clinical remission. In the nonbiologics group, DAS28-ESR decreased from 5.8±0.7 (mean±SD) at base line to 2.1±0.4 at clinical remission. SDAI and MMP-3 also decreased from 29.5±7.9 (mean±SD) and 293.0±191.0 at base line to 1.7±1.1 and 77.5±56.9 respectively at clinical remission. All

**Table 2** Clinical and laboratory characteristics of patients with RA at baseline or clinical remission.

| | Beseline | | In Clinical Remission | |
|---|---|---|---|---|
| | Bio group | Non-Bio group | Bio group | Non-Bio group |
| Age, mean ± SD years | 55.0 ± 17.0 | 60.0 ± 12.0 | | |
| Disease duration, mean ± SD months | 62.3 ± 46.7 | 32.3 ± 9.2 | | |
| No. (%) female | 57.1 | 40 | | |
| MMP-3, mean ± SD | 193.0 ± 175.0 | 293.0 ± 191.0 | 56.6 ± 24.5 | 77.5 ± 56.9 |
| DAS28 (ESR4), mean ± SD | 5.3 ± 1.0 | 5.8 ± 0.7 | 1.5 ± 0.7 | 2.1 ± 0.4 |
| SDAI, mean ± SD | 24.8 ± 11.7 | 29.5 ± 7.9 | 1.2 ± 1.2 | 1.7 ± 1.1 |
| Joint counts, mean ± SD | | | | |
| No. of tender joints | 6.0 ± 3.2 | 6.9 ± 2.9 | 0.1 ± 0.3 | 0.3 ± 0.7 |
| No. of swollen joints | 5.9 ± 3.3 | 6.7 ± 2.8 | 0.4 ± 0.8 | 0.2 ± 0.4 |
| No. (%) ACPA positive | 9 (64.3) | 9 (90.0) | | |
| MRI score, mean ± SD | | | | |
| SAMIS | 17.2 ± 6.3 | 19.0 ± 11.0 | 4.6 ± 4.6* | 10.5 ± 7.7 |
| synovitis score | 5.4 ± 1.8 | 5.1 ± 1.8 | 1.3 ± 1.2 | 2.7 ± 2.1 |
| erosion score | 7.8 ± 5.1 | 10.0 ± 8.4 | 2.9 ± 3.1 | 6.1 ± 5.1 |
| edema score | 4.1 ± 1.8 | 3.2 ± 1.8 | 0.5 ± 0.9* | 1.7 ± 1.5 |

DAS: disease activity score; ESR: erythrocyte sedimentation rate; MMP-3: Matrix Metalloproteinase-3; SDAI: Simplified Disease activity Index; ACPA: anti-citrullinated protein antibody; MRI: magnetic resonance imaging; * $P<0.05$ versus patients in nonbiologics treatment.

patients satisfied both the DAS28-ESR and the SDAI remission criteria (DAS28-ESR score < 2.6, SDAI score < 3.3). There were no significant differences in DAS28, SDAI, and MMP-3 between the biologics group and the nonbiologics group (Figure 1).

Assessment of MRI score. In the biologics group, SAMIS decreased from 17.2 ± 6.3 (mean± SD) at base line to 4.6 ± 4.6 at clinical remission. Synovitis score, erosion score and bone edema score also decreased from 5.4 ± 1.8 (mean± SD), 7.8 ± 5.1 and 4.1 ± 1.8 at base line to 1.3 ± 1.2, 2.9 ± 3.1 and 0.5 ± 0.9 respectively at clinical remission. In the nonbiologics group, SAMIS decreased from 19.0 ± 11.0 (mean± SD) at base line to 10.5 ± 7.7 at clinical remission. Synovitis score, erosion score and bone edema score also decreased from 5.1 ± 1.8 (mean± SD), 10.0 ± 8.4 and 3.2 ± 1.8 at base line to 2.7 ± 2.1, 6.1 ± 5.1 and 1.7 ± 1.5 respectively at clinical remission. SAMIS and bone edema score in the biologics group were significantly lower than that in the nonbiologics group. However, there were no significant differences in the erosion and synovitis score between the biologics group and the nonbiologics group at clinical remission (Figure 2).

Case presentation. MRI findings of patients with RA receiving IFX (case 1 in table 1) or FK506 (case 2 in table 1) were shown in figure 3. At baseline, high-signal intensity on T2-weighted images, consistent with bone edema, were observed in both patient treated with IFX and FK506. At clinical remission, the high-signal intensity disappeared in the patient treated with IFX. On the other hand, the high-signal intensity of bone edema were detected in the patient treated with FK506.

## Discussion

Biological treatment of rheumatoid arthritis patients, such as anti-TNFα agents, has been shown to improve their clinical course and delay or inhibit its structural destruction [9, 10]. Clinical remission is considered a realistic therapeutic target in RA. However, recent studies have shown that radiographic structural progression may be observed after clinical remission, suggesting that there is ongoing disease activity. Recent studies have demonstrated that the imaging modalities such as MRI detected residual inflammatory activity in clinical

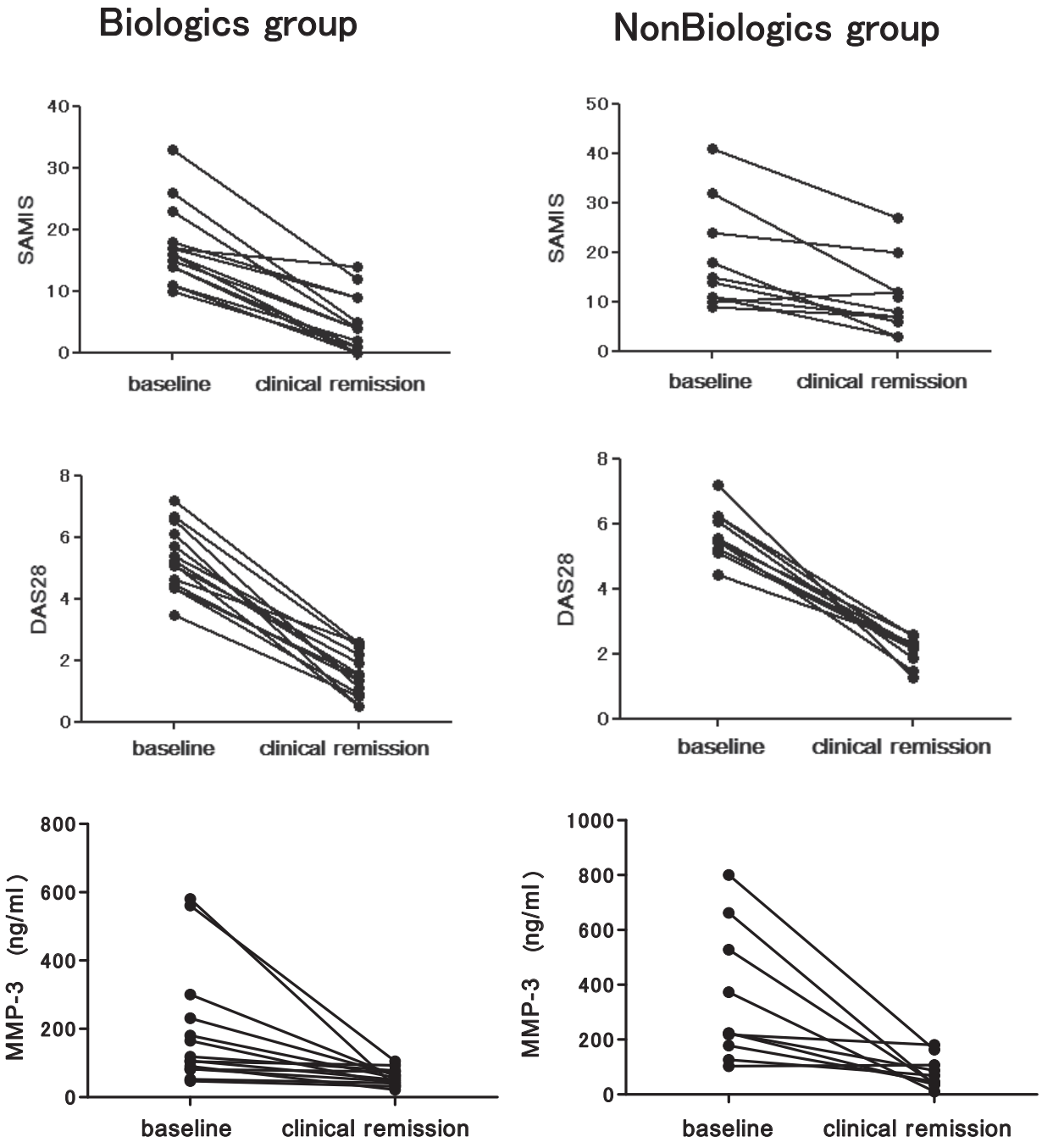


**Figure 1** Serial changes in SAMIS, DAS28 and MMP-3 between baseline and clinical remission.

remission state of RA patients. However, there are few comparative studies on the subclinical inflammation between biologics and nonbiologics treatment judged by MRI, when patients have reached clinical remission.

In this study, subclinical MRI inflammations were identified both in biologics group and nonbiologics group at clinical remission. SAMIS as MRI inflammation in nonbiologics group was significantly higher than that in biologics group. In addition, bone edema score of SAMIS but not erosion score and synovitis score in nonbiologics group was significantly higher than that in biologics group. Our results suggested

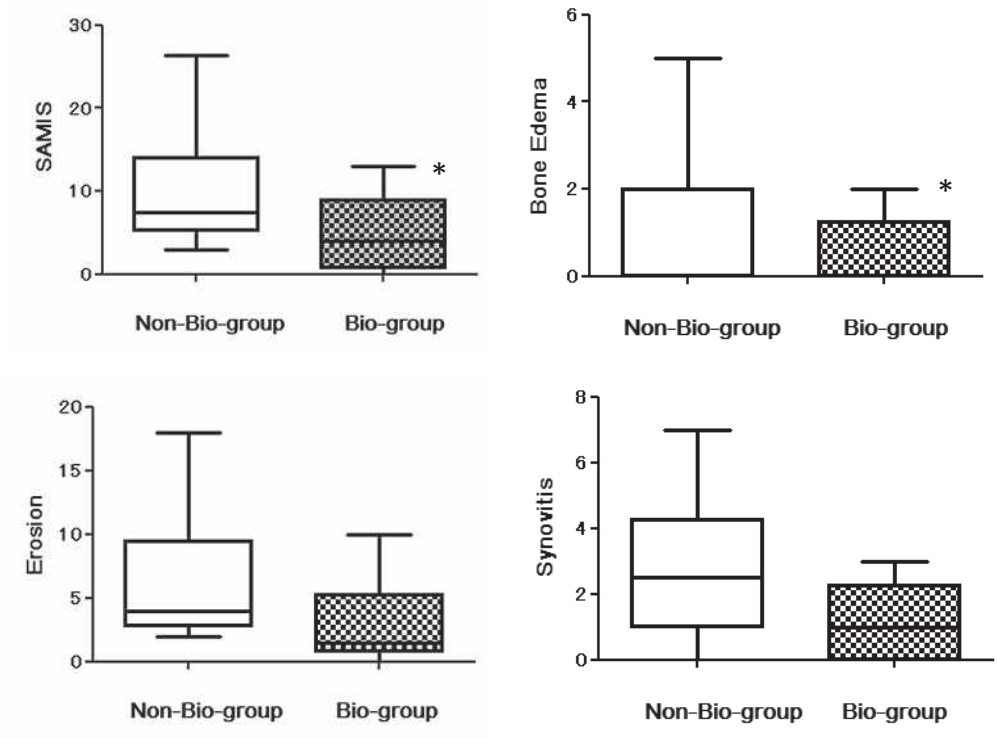


**Figure 2** Imaging assessment of SAMIS in clinical remission.
*P<0.05 versus patients in nonbiologics treatment.

that biologics treatment might be superior to nonbiologics treatment to suppress subclinical inflammation determined by MRI. Because subclinical inflammation may contribute to structural progression in RA patients at clinical remission, the assessment of synovitis by MRI imaging with accurate quantification is important to prevent radiographic progression, and the assessment may provide additional objective information to decide exchange, reduction or discontinuation of therapy.

Bone edema of MRI imaging corresponded to localized bone marrow inflammatory infiltrates suggesting that bone edema plays a role in the inflammatory process of RA [11, 12]. Bone edema is associated with inflammatory cellular infiltrate involving the subchondral bone [13]. Therefore bone edema of MRI imaging is considered to be a pre-erosive area. Furthermore, MRI bone edema has been shown to be a predictor of radiographic damage [14]. Our data suggested that biologics treatment significantly suppressed bone edema in clinical remission, compared with nonbiologics treatment. This finding indicated that treatments of biologic agents to suppress bone edema were important to prevent bone destruction.

In conclusion, the present study supports that treatments of biologics suppress bone edema of MRI imaging and regulate subclinical inflammation. The regulation of subclinical inflammation by treatments of biologics might lead to prevention of bone destruction and improvement of patient outcome.

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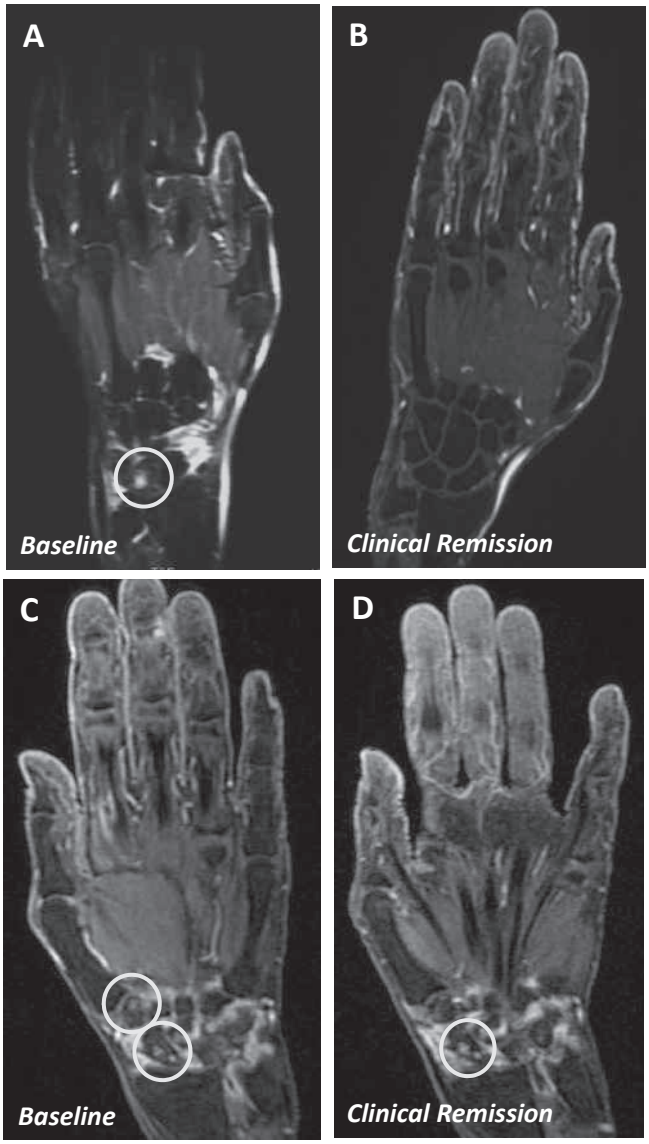


**Figure 3** Bone edema of MRI imaging in patients with rheumatoid arthritis receiving biologics (A and B) or nonbiologics (C and D). At baseline, high-signal intensity on T2-weighted images (open circle), consistent with bone edema, was observed in both patient treated with IFX (A) and FK506 (C). At clinical remission, the high-signal intensity disappeared in a patient treated with IFX (B). On the other hand, the high-signal intensity of bone edema were detected in a patients treated with FK506 (D).

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