phenotype; however, small individual locus effects with ORs in the range of 1.1–1.2 as for other chronic diseases may well be plausible for knee OA, explaining the paucity of other significant hits despite the reasonable large-scale effort. These findings highlight that even larger collaborative studies and improved standardisation of the phenotypes are needed to better understand and identify further genetic variants of OA.

Moreover, even though we were able to accumulate a large sample size, the power of the study to detect very small effect sizes in the range of 1.05–1.15 is inadequate. For example, identification of a GWS signal with an effect size of 1.15 and minor allele frequency of 20% with 80% power would require almost 7000 additional cases of knee OA.

Our results confirm that the 7q22 chromosomal region confers risk for knee OA which, along with our functional work, implicates six possible genes. Further in-depth genetic analysis of the locus including deep sequencing of the region and functional work including in vitro assays and animal models will be required to deepen our understanding of the underlying molecular pathways associated with the disease.

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Meta-analysis of genome-wide association studies confirms a susceptibility locus for knee osteoarthritis on chromosome 7q22

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ORIGINAL ARTICLE

Radiographic progression of cervical lesions in patients with rheumatoid arthritis receiving infliximab treatment

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Abstract We evaluated radiographic change in the cervical lesions of 47 RA patients receiving continuous infliximab therapy for at least 1 year. Infliximab treatment had been initiated between November 2003 and December 2007. Patients who were progressive and non-progressive in terms of RA cervical lesions were compared. Matrix metalloproteinase 3 (MMP3) values improved significantly only in non-progressive patients within the 1-year treatment window. Cervical lesion progression was suppressed in 19 of the 23 patients (83%) showing a good response to infliximab treatment and occurred in 16 of the 24 patients (67%) showing a moderate response. This difference was shown to be significant by the Fisher's exact test ($p = 0.002$). In the well-responding patients ($n = 23$) and moderately responding patients ($n = 24$), the respective changes in the cervical lesion parameters within 1 year were: atlanto-dental interval, 0.17 ± 0.49 and 0.54 ± 0.58 mm ($p = 0.013$); spinal cord, -0.17 ± 0.49 and -0.54 ± 0.59 mm ($p = 0.025$); Ranawat value, -0.09 ± 0.29 and -0.42 ± 0.65 mm ($p = 0.032$). Based on these results, we conclude that infliximab treatment can be used to suppress the progression of rheumatoid arthritis (RA) cervical lesions. It is possible that response to infliximab and MMP3 values can be used to predict the progression of these cervical lesions.

Keywords Cervical lesions · Infliximab · Radiographic progression · Rheumatoid arthritis

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Introduction

Cervical lesions (i.e., cervical vertebral lesions) are known to occur at a high frequency as a complication of rheumatoid arthritis (RA). The progression of cervical lesions leads to severe pain in the post-cervical lesion and myelopathy, which in turn result in a deterioration in the daily living activities of RA patients with joint damage in the limbs. Reports of sudden death due to damage to the brain stem and/or upper cervical region have also been reported [1, 2], and a link between the progression of RA cervical lesions and an unfavorable prognosis has been reported in patients who develop myelopathy [3–5].

The recent introduction of biological agents has had a major impact on RA treatment [6]. Anti-cytokine treatments using inhibitors of tumor necrosis factor α (TNF-α) are more clinically effective than those with the disease-modifying antirheumatic drugs (DMARDs) that were in use previously. Specifically, biological agents have been shown to be efficacious in suppressing joint destruction [7]—in contrast to the scarcity of evidence verifying that therapy with any of the DMARDs can suppress joint destruction. As a result, the administration of DMARDs to many patients has been discontinued due to this lack of efficacy in preventing joint destruction [8]. In contrast, the efficacy of TNF-α inhibitors in suppressing joint destruction has been well documented [9–11]. In our clinical practice, we have found TNF-α inhibitors to be effective not only as evidenced by the

various disease indices, such as the disease activity score using 28-joint counts (DAS28) and matrix metalloproteinase 3 (MMP3), but also in terms of radiographic findings, such as those showing the alleviation of subcartilaginous bone destruction and the recovery of joint space.

To date, most clinical studies on the efficacy of biological agents in suppressing joint destruction have concentrated on the small joints in the hands and feet, and their efficacy against cervical lesions has not yet been reported. We have therefore carried out a prospective investigation on patients receiving infliximab with the aim of elucidating its efficacy for inhibiting the progression of RA cervical lesions, as measured by radiography.

Materials and methods

Patients

We prescribed infliximab treatment for 70 Japanese patients with active RA who were undergoing outpatient treatment at the Department of Orthopedic Surgery and Rheumatology, Nagoya University, and who met the diagnostic criteria stipulated by the American College of Rheumatology in 1987 [12]. Treatment with infliximab was initiated between November 2003 and December 2007; the final study cohort of 47 patients had received continuous infliximab treatment for at least 1 year. All patients were concomitantly administered methotrexate and one or more nonsteroidal antiinflammatory drugs (NSAIDs); they were also allowed to take oral doses of steroidal agents up to 10 mg equivalents of prednisolone/day.

Study protocol

The infliximab dose was 3 mg/kg. The first three doses were administered at weeks 0, 2, and 6, and the fourth and subsequent doses were administered at 8-week intervals up to week 54.

Clinical evaluation, which involved the collection of blood and examination of the patients, was carried out at each time point the drug was administered. The clinical endpoints were 28-joint swollen joint and 28-joint tender joint counts, the patient's global assessment of disease activity (using a 100-mm visual analog scale), C-reactive protein (CRP) level, erythrocyte sedimentation rate (ESR), DAS28 (4ESR), and MMP3 level.

X-radiography of the cervical spine was carried out at the initiation of infliximab treatment and at week 54, and the lesions in the cervical spine were evaluated. This evaluation involved assessment of (1) progression of cervical lesions between Week 0 and 54 and (2) risk factors affecting cervical lesion progression.

Radiographic evaluation

The radiographic evaluations of the cervical lesions were made at the initiation of infliximab treatment and at week 54. The atlanto-dental interval (ADI) [13], the space available for the spinal cord (SAC), and the Ranawat value [14] were measured by plain lateral radiographs with the patient in the flexion position, and the anterior atlanto-axial subluxation (AAS) and vertical subluxation of the axis (VS) were evaluated with the patient bending forward. Assessment of these values (in millimeters) was carried out using digital radiography by two rheumatologists (YK and TK) blinded to the results.

Statistical analysis

Statistical analysis was carried out using SPSS, ver. 11.0 for Windows (SPSS, Chicago, IL). The statistical tests used were:

(1) Wilcoxon signed-rank test. This test was used to evaluate correlations between (1) changes that occurred between treatment initiation (week 0) and week 54 in mean ADI, SAC, and Ranawat value (cervical lesion indices) and (2) changes in CRP, DAS28, ESR, and MMP3 between week 0 and 54 in the patient groups classified as progressive and non-progressive, respectively, in terms of cervical lesions.
(2) Mann–Whitney *U* test. This test was used to compare (1) the mean of each clinical parameter at the initiation of infliximab administration between the cervical-lesion progressive and non-progressive groups and (2) the changes in ADI, SAC, and Ranawat value from week 0 (treatment initiation) to week 54 between patients having different levels of response to infliximab at week 54.
(3) Fisher's exact test. This test was used to evaluate the relationship between cervical lesion progression and alleviation of pain based on the criteria stipulated by the European League Against Rheumatism (EULAR) [15].

In the above tests, p values <0.05 were considered to be significant.

Results

Patients' characteristics

The patients' demographic characteristics are shown in Table 1. The study cohort comprised 11 male and 36 female patients, with a mean age of 53.0 ± 13.4 years,

Table 1 Baseline patient characteristics

Characteristic	Total ($n = 47$ patients)
Demographics	
Age (years)	53.0 ± 13.4
Female, *n* (%)	36 (77)
Disease status	
Disease duration (years)	11.0 ± 10.1
RF positive, *n* (%)	38 (81)
Swollen joint count	7.8 ± 5.6
Tender joint count	8.3 ± 5.0
Patient's global assessment of disease activity (mm)	66.6 ± 20.0
CRP (mg/dL)	3.3 ± 2.6
ESR (mm/h)	49.5 ± 30.2
DAS28 (4ESR)	5.71 ± 1.14
MMP3 (ng/mL)	373.2 ± 331.2
Steinbrocker classification stage (I/II/III/IV)	2/9/22/14
Functional class (1/2/3/4)	7/23/17/0
Drug treatments	
Methotrexate (mg/week)	7.2 ± 2.1
Prednisone use, *n* (%)	30 (64)
Prednisone dose (mg/day)	6.7 ± 4.9

Values are given as the mean ± standard deviation SD unless stated otherwise

RF Rheumatoid factor, *CRP* C-reactive protein, *ESR* erythrocyte sedimentation rate, *DAS28* 28-joint disease activity score, *MMP3* matrix metalloproteinase 3

mean disease duration of 11.0 ± 10.1 years, and mean methotrexate dose of 7.2 ± 2.1 mg/week.

Thirty patients (64%) were administered steroids, and the mean dose was 6.7 ± 4.9 mg equivalents prednisolone/day. Clinical findings related to RA were: swollen joint count, 8.3 ± 5.0; tender joint count, 7.8 ± 5.6; patient's global assessment of disease activity, 66.6 ± 20.0 mm; CRP, 3.3 ± 2.6 mg/dL; ESR, 49.5 ± 30.2 mm/h; DAS28 (4ESR), 5.71 ± 1.14; MMP3, 373.2 ± 331.2 ng/mL. Thirty-eight patients (81%) were rheumatoid factor (RF)-positive.

With respect to the Steinbrocker classification, two, nine, 22, and 14 patients were assessed to be at stages I, II, III, and IV, respectively, and seven, 12, and 27 patients were classified into functional classes [16, 17] 1, 2, and 3, respectively. Based on these results, a large proportion of patients (77%; 36) showed radiographic progression at Steinbrocker stage III or higher.

Changes in the ADI, SAC, or Ranawat value from week 0 to 54

The mean ADI changed from 4.1 ± 2.2 mm at week 0 to 4.5 ± 2.3 mm after 1 year of continuous infliximab treatment ($p < 0.001$). During the same period, the mean SAC changed from 17.1 ± 2.5 to 16.7 ± 2.6 mm ($p < 0.001$), and the mean Ranawat value changed from 13.6 ± 2.6 to 13.4 ± 2.7 mm ($p = 0.002$). All of these changes indicate minor but significant disease progression (Fig. 1).

Investigation of cervical-lesion progressive and non-progressive patients

When progression was defined as a ≥1-mm change in one of the radiographic cervical lesion parameters over a 1-year period, 16 (34%), 15 (32%), and 10 (21%) patients showed cervical lesion progression in terms of the ADI, SAC, and Ranewat value, respectively. Twenty patients (43%) showed progression in at least one of these three parameters.

In order to elucidate the factors that affect cervical lesion progression, we compared 27 non-progressive patients and these 20 progressive patients. This comparison revealed

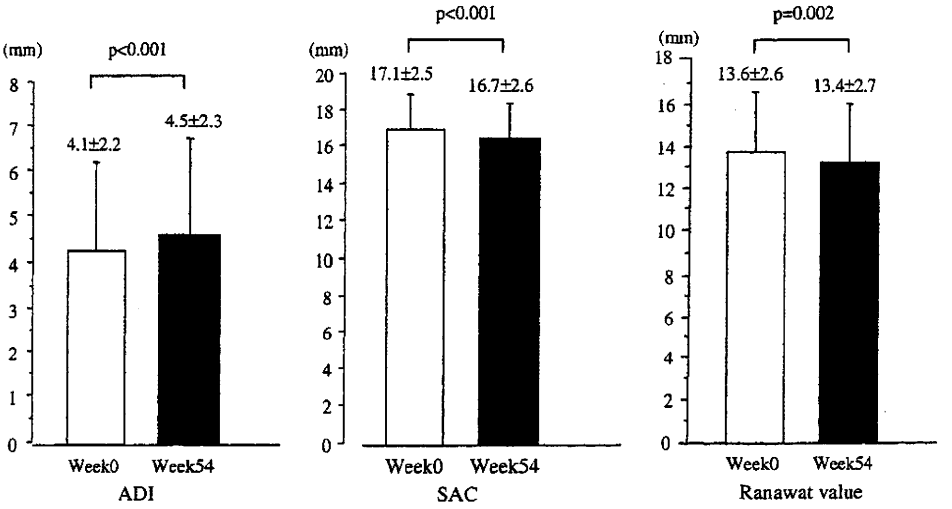

Fig. 1 Changes in the atlanto-dental interval (*ADI*), the space available for the spinal cord (*SAC*), and Ranawat value in rheumatoid arthritis (RA) patients receiving continuous infliximab therapy for a least 1 year. *Week 0* Initiation of treatment, *Week 54* end of study period of continuous infliximab therapy

(non-progressive vs. progressive groups): disease duration, 10.7 ± 10.9 versus 11.4 ± 9.0 years ($p = 0.836$); DAS28 (4ESR) at initiation of infliximab administration, 5.71 ± 1.28 versus 5.72 ± 0.95 ($p = 0.961$); CRP, 3.4 ± 2.7 versus 3.2 ± 2.4 mg/dL ($p = 0.787$); ESR, 48.1 ± 30.6 versus 51.5 ± 30.4 mm/h ($p = 0.705$); MMP3, 423.6 ± 389.4 versus 305.2 ± 222.7 ng/mL ($p = 0.451$). None of these values were significantly different between groups, and no significant differences between groups were observed for Steinbrocker stage or functional class.

The improvement in the clinical parameters of RA disease activity during the 1-year study period was also investigated in both groups. The changes in the CRP, DAS28, and ESR values (non-progressive vs. progressive groups) were: CRP, 3.4 ± 2.7–0.8 ± 1.2 ($p < 0.001$) versus 3.0 ± 2.3 to 1.2 ± 1.2 mg/dL ($p = 0.002$); DAS28, 5.70 ± 1.28 to 3.11 ± 1.27 ($p < 0.001$) versus 5.76 ± 0.94 to 4.18 ± 1.06 ($p < 0.001$); ESR, 48.1 ± 30.6 to 31.9 ± 21.9 ($p = 0.003$) versus 50.9 ± 31.8 to 34.1 ± 28.8 mm/h ($p = 0.008$). These parameters had improved significantly in both groups. In terms of MMP3, the non-progressive group showed marked and significant alleviation in 1 year, from 423.6 ± 389.4 to 165.5 ± 150.8 ng/mL ($p < 0.001$), whereas the change in the progressive group was from 305.2 ± 222.7 to 224.4 ± 109.5 ng/mL ($p = 0.136$), which was not significant (Fig. 2).

Relationship between cervical lesion progression and alleviation according to the EULAR response criteria at week 54

At week 54, the responses to infliximab based on the EULAR response criteria were assessed to be good in 23 patients (49%) and moderate in 24 patients (51%). Whereas cervical lesion progression was suppressed in 19 of 23 patients (83%) showing a good response, progression occurred in 16 of the 24 patients (67%) showing a moderate response. This difference was shown to be significant by the Fisher's exact test ($p = 0.002$).

Comparison between patients responding well and moderately, respectively in terms of changes in ADI, SAC, and the Ranawat value from week 0 to 54

A comparison of patients responding well to infliximab treatment ($n = 23$) with those having a moderate response ($n = 24$) revealed the following changes in cervical lesion parameters within the 1-year treatment window: ADI, 0.17 ± 0.49 (good response) versus 0.54 ± 0.58 mm (moderate response) ($p = 0.013$); SAC, −0.17 ± 0.49 versus −0.54 ± 0.59 mm ($p = 0.025$); Ranawat value, −0.09 ± 0.29 versus −0.42 ± 0.65 mm ($p = 0.032$). All three parameters showed significant progression in the patients with a moderate response to treatment (Fig. 3).

Discussion

Upper cervical lesions, such as the AAS and VS, and middle and lower cervical lesions, such as subaxial subluxation, have long been recognized as complications that occur at a high frequency in RA patients. In general, upper cervical lesions in patients with RA begin with AAS and then progress to VS. Various publications have reported the frequency of AAS and VS in RA patients to be approximately 25% [18–20] and 5–22% [20–22], respectively. VS

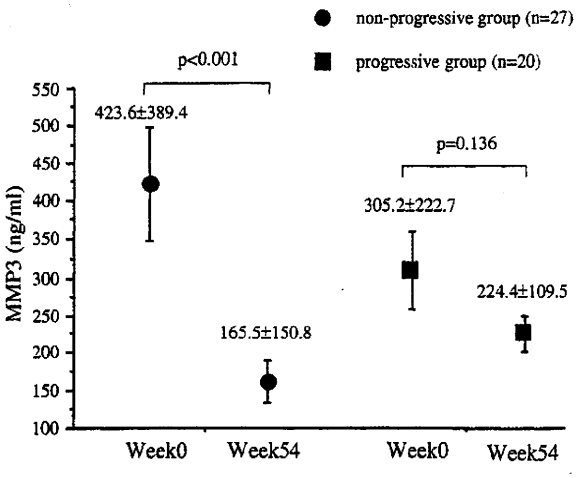

Fig. 2 Comparison of the changes in the matrix metalloproteinase 3 (*MMP3*) value in RA patients of the non-progressive and progressive group, respectively, receiving continuous infliximab therapy for a least 1 year (week 0 to week 54). Data are shown as the mean (*filled squares* or *circles*) ± standard deviation (*bars*)

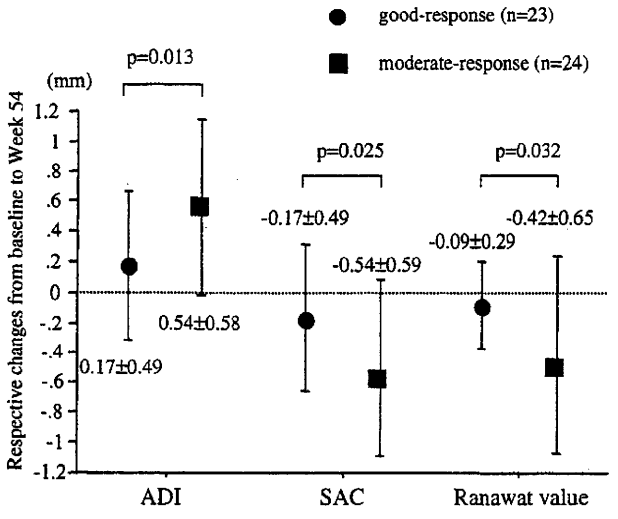

Fig. 3 Respective changes in the ADI, SAC, and Ranawat value in RA patients showing a good response to infliximab therapy between treatment initiation (week 0) and week 54 of treatment and those with a moderate response to treatment

is a particularly serious lesion, and it has been reported to be associated with cases of sudden death [22–26]. Martel and Page [24] reported that the risk of sudden death due to VS is especially high in patients with refractory cervical pain and progressive VS.

Fujiwara et al. reported that, in Japanese RA patients, the frequency of cervical lesions increases with the duration of RA. In their patient cohort, the mean RA duration was 12.3 years, by which time 43% of patients had suffered one or more cervical lesions; this proportion increased to 57% after a duration of 16.5 years and to 60% after 17.5 years. The mean times between RA onset and the appearance of the first lesion have been reported to be 12.7 and 16.5 years for AAS and VS, respectively [27, 28].

The introduction of biological agents has resulted in major changes in RA treatment. Due to the high efficacy of these new agents, clinicians now strongly advise the administration of biological agents from an early disease stage as a means to suppress disease activity and joint damage.

Infliximab is an anti-TNF-α antibody and thus a good representative of a biological agent. Its high clinical efficacy and high efficacy in suppressing joint destruction has been reported in numerous publications [9, 10, 29–32]. In a representative study, the anti-tumor necrosis factor trial in RA with concomitant therapy (ATTRACT), the van der Heijde modification of the Sharp scoring system (vdH Sharp score) [33–37] increased gradually over 1 and 2 years despite the administration of methotrexate at a mean dose of 15 mg/week, whereas joint destruction progression was markedly suppressed in patients receiving infliximab [29]. Further, the vdH Sharp score in patients administered 10 mg/kg infliximab concomitantly with methotrexate showed a negative value [29]. In two other studies, the active controlled study of patients receiving infliximab for treatment (ASPIRE) [10] and the Behandel Strategieen (BeSt) [30], both of which were carried out with patients in the early stages of RA, less than 3 years after onset, infliximab showed excellent efficacy in suppressing joint destruction. However, all infliximab studies published to date have examined its efficacy in suppressing the destruction of the small joints in the hands and feet, and no studies have yet been carried out on its efficacy in suppressing cervical lesion progression.

Robinson et al. [38] reported a case of the clinical effect of infliximab on RA cervical lesions in which symptomatic relief was achieved by 6 weeks in a patient who complained of severe cervical pain and occipital headaches without having AAS. A comparison of the magnetic resonance imaging (MRI) scans of the cervical vertebrae at treatment initiation with those taken 4 months later revealed a reduction in periodontoid rheumatoid pannus formation. Based on these results, these authors propose the necessity of early anti-TNF therapy to prevent the progression of RA cervical lesions. However, this report is a case report, and not a prospective study with many patients having RA cervical lesions.

All of the patients in our study cohort showed significant, albeit minor, progression in the ADI, SAC, and Ranawat value during 1 year of continuous treatment with infliximab. Two probable (partial) explanations for this progression is that our study included numerous patients who had long disease durations and showed radiographic progression and the infliximab and methotrexate doses were low. We compared patients who were progressive and non-progressive in terms of RA cervical lesions and found that CRP levels, DAS28 score, and ESR values had improved significantly in both groups 1 year after the initiation of infliximab treatment, whereas the MMP3 values had improved significantly only in the non-progressive patients. These findings suggest that there is a possibility that MMP3 improvement is an index that predicts the progression of RA cervical lesions. There was no significant difference between the MMP3 values of the two groups at baseline, but these values are still considerably different. It is possible that the significant difference in the non-progressive group that arose between week 0 and week 54 due to high MMP3 values and that a significant difference would be observed in the progressive group when a larger number of patients are available. Therefore, further investigation is needed.

We compared the patients who showed good and moderate responses, respectively, in the EULAR response criteria at week 54 and found a significantly higher suppression of cervical lesion progression in the good responders. In addition, 1 year after treatment initiation, significantly more suppression of the indices of cervical lesion progression (ADI, SAC, and Ranawat value) was observed in the good responders compared to the moderate responders.

On the basis of our results, we suggest that improvement in the MMP3 value is an appropriate index for predicting the progression of RA cervical lesions and hand and foot joint lesions. The high efficacy of infliximab in suppressing joint destruction when it is used to treat early RA suggests that the administration of infliximab at an early stage of the disease will be successful in suppressing the progression of both RA cervical lesions and foot and joint lesions.

Investigations on joint damage in RA generally focus on the hand and foot joints. However, our results suggest that rheumatologists should also pay attention to preventing the progression of RA cervical lesions since such a progression negatively impacts on both the prognosis and daily living activities of RA patients.

This study is the first to investigate the efficacy of infliximab treatment in suppressing the progression of RA cervical lesions in a relatively large patient cohort.

Conclusions

Infliximab treatment can be used to suppress the progression of both RA cervical lesions and lesions of the hand and foot joints. It is possible that response to infliximab and MMP3 improvement can be used to predict the progression of RA cervical lesions.

Conflict of interest statement N. Ishiguro has received speaking fees (less than $10,000) from Mitsubishi Tanabe Pharma Corporation Osaka, Japan. The other authors have declared no conflict of interest.

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ORIGINAL ARTICLE

Influences of anti-tumour necrosis factor agents on postoperative recovery in patients with rheumatoid arthritis

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Abstract The aim of this study is to investigate the influences of the anti-tumour necrosis factor (TNF) agents infliximab and etanercept on the postoperative recovery of patients with rheumatoid arthritis (RA). We also investigated the effects of biologics on wound healing. Patients with RA were split into a TNF group (n=39) that underwent 39 operations and were treated with anti-TNF agents, and a non-TNF group (n=74) that underwent 74 operations and were treated only with conventional disease-modifying antirheumatic drugs. Operations included ankle arthrodesis and total arthroplasty of the hip, knee, elbow, shoulder and ankle. Adverse events (AEs) of surgical wounds, time for complete wound healing, febrile period after operation and recovery parameters after operation (%recovery of haemoglobin (Hb), total protein and albumin at 4 weeks after operation compared with pre-operation levels) were investigated. AEs of surgical wounds occurred in two operations (5.1%) in the TNF group and in five operations (6.8%) in the non-TNF group, but this difference was not statistically significant. There were also no significant differences in the time for complete wound healing and in the length of the febrile period between the two groups. Percentage recovery of Hb was significantly better in the TNF group than in the non-TNF group (96.3% vs. 90.1%, respectively; p<0.05). These results suggest that the use of anti-TNF agents does not cause specific AEs on surgical wounds after elective orthopaedic operations in RA patients and might improve the percentage recovery of Hb due to its prompt anti-TNF effects.

Keywords Anti-tumour necrosis factor agent · Operation · Postoperative recovery · Rheumatoid arthritis · Surgical wound

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Introduction

Anti-tumour necrosis factor (TNF) therapy provides great benefit to patients with rheumatoid arthritis (RA) by inhibiting joint destruction and suppressing inflammation [1, 2]. TNF-α is a proinflammatory cytokine that has numerous effects on both the physiology and the pathology of humans. It plays a key role in the joint pathology of RA patients [3], as well as in the healing of wounds [4–6], and in host defences against bacterial [7–9], viral [10] and mycobacterium infections [11]. According to these reports, anti-TNF therapy might cause a delay in the healing of surgical wounds, increasing the number of postoperative infections. As TNF-α affects general condition of the host, such as general fatigue or febrile condition, Anti-TNF usage may affects postoperative general condition, especially febrile condition, in the patient. However, the clinical influences of anti-TNF agents on wound healing and RA patient postoperative recovery are not well known.

Anti-TNF therapy could be expected to decrease the number of orthopaedic operations, such as total arthroplasty, required for RA patients. However, as many RA patients

have long-term disease and advanced joint destruction, the percentage of patients taking anti-TNF agents and undergoing surgery seems to be increasing. den Broeder et al. reported a threefold increase from 1997 to 22% in 2004 [12]. In our institute (Nagoya University Hospital, Japan), we recorded an increase from 11.5% in 2005 to 52.9% in 2008 in patients treated with anti-TNF agents undergoing orthopaedic operations on large joints.

It is important to understand both the advantages and the disadvantages of anti-TNF therapy for surgical procedures. In this study, we therefore investigated the influences of anti-TNF agents on the postoperative recovery in patients with RA. We also investigated the effects of biologics on wound healing.

Materials and methods

One hundred and thirteen patients with RA who underwent surgical procedures between April 2004 and July 2007 in either Nagoya University Hospital (Nagoya, Japan) or Nagoya Medical Centre (Nagoya, Japan) were included in this study. Only the first surgery for each patient was included in this study. Patients were divided into a TNF group (n=39) that underwent 39 operations and were treated with anti-TNF agents, and a non-TNF group (n=74) that underwent 74 operations and were treated with conventional disease-modifying antirheumatic drugs (DMARDs). The TNF group comprised patients from both institutes, whereas the non-TNF group comprised patients only from Nagoya University Hospital. The anti-TNF agents used were either infliximab (INF) or etanercept (ETA) as adalimumab was not available in Japan during the study period.

The operations included in this study were primary total hip arthroplasty (THA), total knee arthroplasty (TKA), total elbow arthroplasty, total ankle arthroplasty, total shoulder arthroplasty and ankle arthrodesis. Revision surgery and other minor operations, such as foot operations and wrist operations, were excluded.

We investigated the following: (1) the occurrence rate of adverse events (AEs) of surgical wounds, such as wound dehiscence, continuation of discharge and infection. Wound dehiscence is defined wound which is not completely healed in 14 days after operation or wound which needs secondary suture. Infection is defined that culture examination is positive; (2) the period of time taken for complete wound healing, from the date of operation to the removal of surgical staples; (3) postoperative febrile periods (body temperature >37.5°C); and (4) comparison of preoperative and postoperative parameters including haemoglobin (Hb), serum total protein (TP) and serum albumin (Alb). The %recovery of Hb (%Hb), %recovery of TP (%TP) and %recovery of Alb (%Alb) were defined as follows: (4-week postoperative level/preoperative level) × 100%. Additionally, we analysed the results in the THA subgroup or TKA subgroup.

Data were collected from medical records and results were compared between the TNF and non-TNF groups. Anti-TNF agent administration was stopped prior to the operations and restarted after surgical wounds were completely healed. Our protocol of preoperative cessation of anti-TNF agents is 3-4 weeks before operation in case of INF and 1-2 weeks before operation in case of ETA. Mean periods from last administration of anti-TNF agents to operation were 29.8 days for INF and 9.6 days for ETA.

Data were expressed as the mean value ± standard deviation. The Mann-Whitney U test was used to evaluate the significance of differences in continuous variables because not all data were normally distributed. Fisher's exact test was used to evaluate the significance of differences in proportions. $P<0.05$ was considered statistically significant.

Results

The baseline characteristics of patients at the time of the operations are shown in Table 1. The total numbers of operations in the TNF group and the non-TNF group were 39 and 74, on 39 and 74 patients, respectively. Only the first operation for each patient was included. No patients belonged to both groups. The difference in mean age at the time of operation was statistically significant: 58.9± 9.0 years in the TNF group and 62.6±9.1 years in the non-TNF group ($P<0.05$). More patients of stage IV were included in TNF group than non-TNF group ($P<0.05$). Methotrexate was more frequently used in TNF group than non-TNF group ($P<0.05$). The operation performed is shown in Table 2.

AEs of surgical wounds occurred after two operations in the TNF group (5.1%) and after five operations in the non-TNF group (6.8%), which was not a statistically significant difference by Fisher's exact test (P=1.0000). Odds ratio was 0.7459 (95% confidence interval; 0.1380-4.0336). Although most AEs of surgical wounds were wound dehiscence and continuation of discharge that were healed by conservative treatment, postoperative infection occurred after one TKA operation in the TNF group. The patient was a 68-year-old female who received preoperative treatment of INF (200 mg/infusion), methotrexate (6 mg/week) and oral predonisolone (5 mg/day). The last administration of INF was 21 days before the operation. The patient had a high fever immediately after the operation date, and a discharge continued from the wound although no bacteria were detected by culture examinations. Finally, surgical debridement without removal of the implant was performed

Table 1 Baseline characteristics of patients

Characteristics		TNF group (n=39)	Non-TNF group (n=74)	P value[a]
Gender	Male	7	9	
	Female	32	65	
	%female	82.1%	87.8%	0.4087
Age at operation, year (range)		58.9±9.0 (31-73)	62.6±9.1 (30-77)	0.0308
RA duration, year (range)		13.5±7.8 (4-32)	16.5±11.7 (1-51)	0.5720
Stage (Steinbrocker)				
%stage III		18.8%	52.7%	0.0249
%stage IV		81.2%	47.3%	
Class (Steinbrocker)				
%class 2		18.8%	20.3%	1.0000
%class 3		81.2%	68.9%	
%class 4		0	10.8%	
%RF positivity		69.2%	67.1%	1.0000
Mean CRP (mg/dl)		1.56±1.49	1.99±2.41	0.6424
Mean ESR (mm/hour)		41.1±34.7	41.9±24.2	0.5982
%MTX use		92.3%	50.0%	0.0001
Mean PSL usage (mg/day)		4.3±3.6	2.8±3.0	0.0871
Anti-TNF usage				
Infliximab		24		
Etanercept		15		

[a] Mann-Whitney U test was used in case of continuous variables. Fisher's exact test was used in case of dichotomous variables

TNF tumour necrosis factor, *RA* rheumatoid arthritis, *RF* rheumatoid factor, *CRP* C-reactive protein, *ESR* erythrocyte sedimentation rate, *MTX* methotrexate, *PSL* predonisolone

and *Capnocytophaga* species was detected from a synovia specimen. Ampicillin/sulbactam at 6 g/day was administrated for 4 weeks and the infection settled down well.

The average time from the date of operation to the removal of surgical staples was 10.9±1.2 days in the TNF group and 10.8±1.3 days in the non-TNF group, which was not a statistically significant difference. The postoperative febrile periods (body temperature ≥37.5°C) were 2.6±2.2 days in the TNF group and 2.9±1.7 days in the non-TNF group, which was also not a statistically significant difference.

The results for postoperative anaemia and recovery are shown in Fig. 1. The preoperative levels of serum Hb, serum TP and serum Alb in the TNF group were 11.2±2.0 g/dl, 7.3±0.8 g/dl and 3.8±0.4 g/dl, respectively. The preoperative levels of serum Hb, serum TP and serum Alb in the non-TNF group were 11.6±1.8 g/dl, 7.1±0.6 g/dl and 3.8±0.5 g/dl, respectively. There were no statistically significant differences in the three parameters between the TNF and non-TNF groups. There were also no statistically significant differences in %TP and %Alb between the TNF and non-TNF groups, with %TP values of 100.8±9.5% and 100.8±9.2% and %Alb values of 98.9±13.5% and 98.0±11.3%, respectively. However, the %Hb was significantly

Table 2 Performed operations

operation	TNF group	Non-TNF group
Total number	39	74
TKA	14	51
THA	13	17
TEA	8	4
AD	3	1
TSA	1	0
TAA	0	1

TNF tumour necrosis factor, *TKA* total knee arthroplasty, *THA* total hip arthroplasty, *TEA* total elbow arthroplasty, *AD* ankle arthrodesis, *TSA* total shoulder arthroplasty, *TAA* total ankle arthroplasty

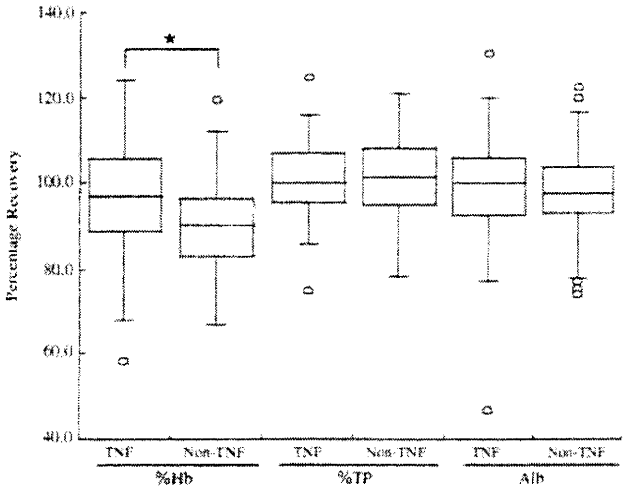

Fig. 1 %recovery of serum Hb, serum TP and serum Alb. Percentage recovery was defined as follows: (4-week postoperative value/preoperative value) × 100 (%). *Asterisk* statistically significant differences in %Hb (P<0.05, Mann-Whitney U test)

higher in the TNF group (96.3±14.3%) than in the non-TNF group (90.1±11.5%; P=0.0156).

We analysed the influence of anti-TNF agents on the healing of surgical wounds and postoperative recovery in the THA subgroup (30 operations in total, 13 in the TNF group and 17 in the non-TNF group) and the TKA subgroup (65 operations in total, 14 in the TNF group and 51 in the non-TNF group; Table 2). The AE occurrence rates of surgical wounds were 0.0% in the TNF group and 0.0% in the non-TNF group in the THA subgroup. The AE occurrence rates of surgical wounds were 7.1% (one operation) in the TNF group and 7.8% (four operations) in the non-TNF group in the TKA subgroup. There was no statistically significant difference between the two groups. Odds ratio was 0.9038 (95% confidence interval; 0.0928-8.7992).

The febrile period after the operation was 3.5±2.0 days vs. 3.1±1.9 days in the THA subgroup and 2.6±2.5 days vs. 2.9±1.7 days in the TKA subgroup, comparing the TNF and non-TNF groups, respectively. There were no statistically significant differences between the two groups in either subgroup. The %Hb, %TP and %Alb were 101.0± 14.4% vs. 83.8±10.0%, 103.5±10.5% vs. 100.3±9.3% and 100.3±10.1% vs. 94.7±11.7% in the THA subgroup, comparing the TNF and non-TNF groups, respectively (Fig. 2a). There was a statistically significant difference between the %Hb of the TNF and non-TNF groups (P= 0.0016), but not between the other two parameters. The %Hb, %TP and %Alb were 92.6±16.9% vs. 92.0±11.5%, 101.1±10.7% vs. 101.0±9.6% and 98.8±19.4% vs. 99.3± 11.7% in the TKA subgroup, comparing the TNF and non-TNF groups, respectively (Fig. 2b). There were no statistically significant differences in any parameter between the TNF and non-TNF groups.

Discussion

In this study, we showed that anti-TNF agents could be beneficial in post-operative recovery during orthopaedic procedures such as total joint arthroplasty. To our knowledge, this is the first report to study the influences of anti-TNF agents on the postoperative recovery of patients with RA.

Anaemia of chronic disease (ACD) is one of the most common comorbidities of RA [13]. Inflammatory cytokines such as TNF-α and interleukin 6 play an important role in the pathogenesis of ACD [14], with increased levels of TNF-α inducing apoptosis in erythroblasts, thus decreasing their numbers. Administration of anti-TNF antibodies has been found to decrease apoptosis of erythroid cells [15]. The present study suggests that anti-TNF agents could prevent these processes occurring in active RA patients undergoing joint surgery, and might lead to improved recovery of Hb levels. Indeed, anti-TNF agents could have more beneficial effects on post-operative recovery than conventional DMARDs.

Influences of TNF-α on wound healing have been documented in several in vitro studies. Mooney et al. reported that the application of recombinant TNF-α improved wound

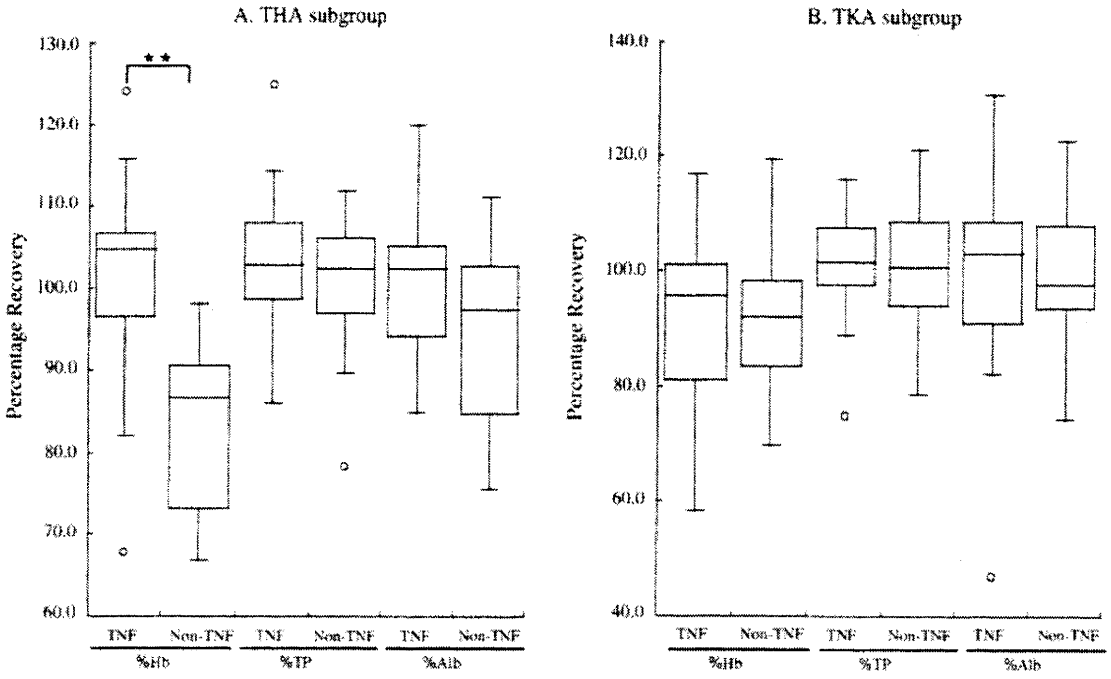

Fig. 2 Comparison of %recovery in THA (A) and TKA (B) subgroups. *Double asterisk* statistically significant differences in %Hb in THA subgroup (P<0.01, Mann-Whitney U test)

healing of normal and adriamycin-impaired mice [4]. By contrast, Salomon et al. found that local TNF application impaired both wound healing and collagen gene expression in rats [5], while Mori et al. showed that TNF receptor p55-mediated signals negatively affected wound healing by reducing angiogenesis and collagen accumulation in TNF receptor p55-deficient mice [6]. Although the influences of TNF-α on wound healing are therefore controversial, these results suggest that modulation of TNF-α affects the collagen synthesis necessary for wound repair.

Animal model studies have shown that TNF-α is involved in the host defence mechanism against bacterial infection [7–9]. This suggests that excessive decreases in the effects of TNF-α might increase the number of bacterial infections, and that it might therefore be safe to stop the administration of anti-TNF agents for an appropriate period before an operation. The American College of Rheumatology 2008 recommendations for the use of nonbiologic and biologic DMARDs in RA suggest that biologic agents should not be used during the perioperative period for at least 1 week before and after surgery [16]. The report also recommends that a period of discontinuation should be tempered by the half-lives of the agent used. As INF has a longer half-life than ETA (7.7–9.5 days vs. 102±30 h), it is reasonable that a longer time period is given from the last administration of INF before surgery than that with ETA. The Japanese guidelines advise that surgery should be delayed until a sufficient time has elapsed from the last administration of anti-TNF agents [17]. Although no definite time is stated in these recommendations, the biological half-lives of the drugs should be taken into consideration. In the present study, the mean time periods from the last administration of anti-TNF agents before surgery were 29.8 days for INF and 9.6 days for ETA. Although Talwalkar et al. reported that the continuation of anti-TNF agents in the perioperative period did not increase either the rate of infection or the complication rate [18], we decided to use a safe and appropriate period for stopping agent administration.

In clinical studies, the influences of anti-TNF agents on the healing of surgical wounds or the manifestation of infection are controversial. Bibbo et al. reported that the use of anti-TNF agents might be safely undertaken in the perioperative period without increasing healing risks or infectious complications in RA patients undergoing elective foot and ankle surgery [19]. den Broeder et al. investigated postoperative surgical site infections in 1,219 operations carried out in 768 patients, and found that the crude infection risks were 4.0%, 5.8% and 8.7% in patients who did not use anti-TNF agents, patients who did but then stopped and patients who continued anti-TNF preoperatively, respectively [12]. Although an increase in infection rate was associated with anti-TNF agent use, the authors concluded that anti-TNF agents were not an important risk factor for surgical site infection. Wendling et al. reported that an interrupted use of anti-TNF treatment in patients with RA undergoing orthopaedic and non-orthopaedic surgery did not increase frequency of adverse events [20]. These studies, along with our own, suggest that the use of anti-TNF agents is not disadvantageous in terms of AEs such as infection. By contrast, Giles et al. reported that anti-TNF agents increased the rate of infection in elective orthopaedic operations [21].

There are some limitations of the present study. At first, the method used is a retrospective cohort study which can lead to information bias, as not all consequences have been measured in a prospective and standardised way. Although future studies should be of a prospective design, we think that a retrospective study can show the results in the real-world clinical setting and show useful information. Second limitation is that sample size is small. A prospective study based on a larger sample size to ascertain whether the use of anti-TNF agents is wholly advantageous. Third limitation is confounding by indication. Patients are RA patients that either use anti-TNF or are non anti-TNF users. This can lead to confounding by indication, as patients that use anti-TNF can have a different risk of infection and wound healing problems by virtue of the severity of the RA itself, not due to the difference of the treatment. A study which includes random cessation of anti-TNF treatment is necessary in the future. Forth limitation is the problems of cessation of anti-TNF agents before operation. Because cessation of anti-TNF agents, 3-4 weeks in case of INF and 1-2 weeks in case of ETA, cause the reduction of effects of anti-TNF agents at the operation date, the results of this study may not show the accurate influence of anti-TNF agents on surgical wounds and postoperative recovery. This is also a limitation from a retrospective study in the real-world clinical setting.

In conclusion, the present findings suggest that the controlled use of anti-TNF agents causes no specific AEs on surgical wounds after elective orthopaedic operations in RA patients and might improve the recovery from post-operative anaemic conditions due to anti-TNF effects on bone marrow.

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Exploring the link between depression and rheumatoid arthritis: prospects for optimal therapeutic success

"Should rheumatologists be responsible for the management of depressive symptoms of their patients? The answer is definitely yes."

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According to the guidelines by the American College of Rheumatology, the goals of managing rheumatoid arthritis (RA) are to prevent joint damage and loss of function, and to decrease pain [1]. Should rheumatologists be responsible for the management of depressive symptoms of their patients? The answer is definitely yes.

Depression is a common comorbidity in patients with RA, with a prevalence of 13–20% [2,3]. Patients with RA are twice as likely to be depressed as people in the general population [4]. Depression is commonly associated with pain [5], which is a chief complaint of RA, along with poor prognosis [4]. The importance of assessing depression among RA patients has been repeatedly proposed [3,6]. However, according to a recent article by Sleath *et al.*, rheumatologists rarely discuss depression with their patients during medical visits [7].

"Data indicated that both inflammation and depression severity were significantly associated with pain, even after adjustment for clinical covariates in regression analyses."

We examined the association between pain and depression in 218 outpatients with RA [8,9]. The level of inflammation was measured by C-reactive protein (CRP), and depression was assessed using the Beck Depression Inventory (BDI-II), a validated self-report scale of depression [10]. Data indicated that both inflammation and depression severity were significantly associated with pain, even after adjustment for clinical covariates in regression analyses. In logistic analysis, the combined effects of inflammation and depression in the presence of severe pain were linearly increased by the CRP level and depression severity, independently.

Two different kinds of persistent pain are known to exist: nociceptive/inflammatory pain and neuropathic pain [11]. While nociceptive/inflammatory pain is caused by injury or inflammation-stimulating nociceptive receptors at the periphery of the nervous system, neuropathic pain occurs as a result of lesion or dysfunction of the peripheral or central nervous system [12]. Our findings support the coexistence of the two kinds of pain in RA patients. Nociceptive pain is responsive to anti-inflammatory therapy, whereas neuropathic pain is complicated and difficult to treat. Antidepressant and antiepileptic drugs are commonly prescribed for neuropathic pain [13]. Also, nonpharmacological treatments, such as cognitive-behavioral therapy, are solely or additionally available. However, there is no sovereign remedy for neuropathic pain. Patients should be treated physically and mentally, based on the formulation of each patient's problems [5].

Rheumatoid arthritis is a chronic inflammatory disease, the etiology of which is not fully understood. There has been no fundamentally curative therapy for RA for a long time. Currently, dramatic improvements in biologic and nonbiologic disease-modifying antirheumatic drugs (DMARDs) enable us to achieve remission in most cases. When treatment is started at an early stage, an increasing number of RA patients can obtain disease control without joint damage. If DMARD therapy is started without delay, the prevalence of depression among RA patients might be decreased and the impact of depression on RA prognosis could be minimized. However, DMARDs have their side effects. Due to their toxicities, they cannot be prescribed for patients who have liver and/or kidney dysfunctions. Patients suffering from infectious diseases are also unable to take DMARDs. Some patients must discontinue DMARD therapy due to severe side effects or cost constraints.

We are at the next stage of considering ways to support those patients who cannot benefit from DMARDs. Support for the psychological

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problems for such patients is essential. Moreover, since depression is known to be associated with poor adherence to drug treatment, patients who were experiencing depressive symptoms before the initiation of therapy, are more likely to have problems. Therefore, to achieve the best RA management, psychological assessment and support are equally necessary for all patients.

It is argued that rheumatologists do not have enough time to assess their patients' depressive symptoms in the clinic [6]. However, simple questionnaires such as the Primary Care Evaluation of Mental Health Disorders Patient Health Questionaire (PHQ-9) [14], Hospital Anxiety and Depression Scale (HADS) [15] and BDI-II [10] exist, which are validated depression screening tools and take only 2–5 min to be completed in the primary care setting [16]. Additionally, two specific questions are commonly used to screen for depression [17]. First, for example, a patient can be asked, 'during the past month, have you often been bothered by feeling down, depressed, or hopeless?', or 'during the past month, have you often been bothered by little interest or pleasure in doing things?' If patients endorse any of the two questions, they may at least have mild depression and should be assessed further.

> *"The association between systemic inflammation and depression has attracted attention because they share some physiological process and may have some common role in the development of cardiovascular disease."*

According to the consensus statement of the UK experts in the management of depression in general practice [18], patients who have moderate-to-severe depression should take antidepressant medication. It is not conclusively known whether patients with mild depression should be treated with antidepressants. Counselling and psychosocial approaches are necessary for all patients who endorse depressive symptomatology.

Some small clinical trials have reported the benefits of tricyclic antidepressants in the management of depression and pain control among RA patients, and most selective serotonin reuptake inhibitors (SSRIs) and serotonin–noradrenaline reuptake inhibitors are suggested for the treatment of fibromyalgia syndrome [19]. Compared with traditional tricyclic antidepressants, SSRIs and serotonin–noradrenaline reuptake inhibitorss are less toxic and have fewer side effects; therefore, they are popular among elderly and physically ill patients. However, there is little evidence regarding treatment of RA patients using these medications. Further controlled studies are required to determine the optimal use of antidepressants for the management of depression and pain control among RA patients.

The association between systemic inflammation and depression has attracted attention because they share some physiological processes and may have some common role in the development of cardiovascular disease (CVD) [20]. Experimental studies support the bidirectional associations between depression and inflammation involving the neuroendocrine and autonomic nervous systems [21]. RA patients commonly experience both depression and inflammation. Moreover, CVD is a common comorbidity among RA patients and is the leading cause of premature death among RA patients. Although the mechanism of increased CVD risk among RA patients has not been fully disclosed, it is suggested that chronic systemic inflammation plays a major role [22]. Depression is an established risk factor for the development and prognosis of CVD. Even though depression and CVD are both common comorbidities in RA patients, depression has rarely been discussed in relation to the increased risk of CVD in RA. A recent empirical study suggests a possibility of SSRIs as anti-inflammatory drugs for RA patients [23]. RA patients may experience additional benefits from antidepressants in decreasing depressive symptoms that may prevent premature CVD mortality.

In conclusion, rheumatologists must pay attention to their patients' depressive symptoms and provide appropriate guidance, including referrals to specialists, if necessary. Future studies should help clarify the best way to manage depression associated with RA and the extent to which such treatment may benefit RA patients.

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各論

8．変形性膝関節症の治療：関節内注射(ヒアルロン酸，ステロイド)の有効性と使い方

石黒 直樹

KEY WORD

- Hyaluronic acid
- osteoarthritis
- intra-articular injection
- steroid

SUMMARY

■変形性膝関節症(OA)の治療は，①関節症状に対する治療，すなわち，疼痛抑制治療(symptom modifying effect)と，②関節軟骨破壊抑制治療(structure modifying effect)から成立する．ヒアルロン酸(HA)は関節液中では関節液粘張性の保持に重要で，低分子化は潤滑機能の低下に直結する．HAの消失は摩耗や関節軟骨破壊の大きな原因となる．関節内に投与されたHAによる関節液の粘性改善は薬効を考える上で大きな要素である．一方，関節注入HAに生物学的な意義を評価し，関節軟骨の破壊が抑制されるとの議論もある．ステロイド関節注射は，短期的にはHA注射に比較して効果に勝るが，合併症が多く，かつ全身的な影響も無視できない．頻回投与を避け，必要最低限の回数に留めるべきである．OAHA注入療法はEBMの点からも推奨できる治療である．

はじめに

高齢化社会では変形性膝関節症(以下OA)は罹病率が高く，極めて重要な疾患である．臨床症状を伴い，日常生活で問題となるようなOAは一般的に膝関節に多くみられる．OAは，X線診断と臨床症状が時として乖離を示すことが知られている．OAは主に軟骨局所における機械的ストレス，代謝変化，加齢，遺伝的背景などの複合的な原因をもとに発生する変性疾患である．炎症に伴う関節液の貯留や滑膜におけるヒアルロン酸(以下HA)合成の低下により，軟骨面における潤滑が不良となり，これが機械的ストレスの増大につながり，軟骨変性が加速させる．OAでは，軟骨の破壊と骨棘形成などの修復反応が同時に進行する複雑な病態を示す．

一般的に進行は長期にわたり，病初期には明確な症状を起こさないままに過ごし，進行して関節症状，特に炎症，水腫などを主訴に，医師を訪れて診断される例も多いと考えられる．このことは軟骨組織が神経終末を欠き，軟骨の損傷や破壊だけでは疼痛を感じないことと関連をもつと考えられる．OAの痛み症状は軟骨組織以外の滑膜，骨，関節包でみられる炎症が原因で起こっている．しかし，この炎症を起こした原因が軟骨の破壊であることは忘れてはならない．OAに対して局所療法としての関節内注射は，日常臨床ではしばしば用いられる治療手段であ

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