Characteristics of patients with rheumatoid arthritis in clinical remission: the many aspects of DAS28 remission

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ABSTRACT

Objective. *The aim of this study was to observe the clinical characteristics, including the extent of foot and ankle involvement, of Korean patients with rheumatoid arthritis (RA) in remission, defined as Disease Activity Score in 28 joints (DAS28) <2.6.*

Methods. *Data from a registry of RA patients who visited a rheumatology clinic of a university-affiliated hospital and who were regularly evaluated with DAS28, including the ankle and foot metatarsophalangeal (MTP) joints were enrolled. Patients who were treated with disease-modifying anti-rheumatic drugs for at least three months and who were in DAS28 remission were included in this study.*

Results. *Two hundred and thirteen episodes of DAS28 remission were observed in 147 patients. The mean DAS28 value at the time of remission was 1.84 (range, 0.14–2.59). The mean numbers of swollen joints and tender joints (of the 28 joints examined for DAS28) at the time of remission was 0.4 (range, 0–6) and 1.5 (range, 0–13), respectively. Overall, 11.7% and 38% of the patients in clinical remission had foot MTP/ankle swollen and tender joints, respectively. Additionally, 7% and 8.9%, respectively, of the patients in clinical remission had foot MTP/ankle swollen and tender joints without any involvement of the 28 joints included in the DAS28.*

Conclusion. *Our results show that RA patients in DAS28 remission frequently have residual disease activity in the ankle and foot joints. Given that forefoot disease activity can lead to joint damage and disability with respect to weight-bearing activities, these joints should be included in the clinical examination.*

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory arthritis characterised by multiple small-joint involvement and significant disability (1). The ultimate therapeutic goals are to relieve pain, slow the progression of joint destruction, and achieve remission. Recently, a treatment-to-target strategy for RA has been recommended to improve the treatment outcomes and to prevent joint damage and physical disability (2, 3). Clinical remission is, thus, becoming the goal for the treatment of RA (4).

As disease activity is a good predictor of joint damage, tight control of RA based on a pre-specified disease-activity index instead of the traditional treatment strategy is gaining importance in terms of achieving better clinical outcomes (5-8). Currently, several criteria for disease activity and remission exist. The American College of Rheumatology (ACR) remission criteria represented the first attempt to define remission in RA (9). However, the ACR remission criteria have not been widely adopted in clinical practice because they contain ambiguous items, such as fatigue, and are so stringent that few patients meet the criteria (10, 11). Additionally, the ACR criteria measure the relative changes from previous levels and do not reflect disease activity at the moment of measurement. Disease activity scoring systems that include a 28-joint count (DAS28) or a 44–joint count (DAS) are also used to assess disease activity (12–18), and DAS28 <2.6 or DAS <1.6 have been used to define remission in RA (19, 20). Although DAS28 has been used widely in both clinics and research settings owing to its relative ease of application, the remission criteria based on it have been criticised because they represent low disease activity rather than remission, given the remaining swollen or tender joints (21, 22). In particular, although ankle and foot joints, such as the metatarsophalangeal (MTP) joint, are commonly involved in RA, DAS28 does not include these joints. In this respect, Landewe *et al.* (22) have suggested that DAS28 remission with a cutoff level of 2.6 has insufficient construct validity and should be used with caution.

The aim of the present study was to examine the clinical profiles of Korean patients with RA in DAS28 remission. Additionally, the extent of foot and ankle involvement in patients with DAS28 remission was explored.

Patients and methods

From August 2010, patients with RA who fulfilled the 2010 ACR criteria (23) and who visited the Rheumatol-

ogy Clinic of Hallym University Sacred Heart Hospital were evaluated every 3–6 months using the DAS28 and evaluations of ankle and ten MTP joints. This study utilised clinical data from a registry of these RA patients, stored as electronic medical records. Patients who were treated with disease-modifying anti-rheumatic drugs (DMARDs) for at least three consecutive months and who were in DAS28 remission (DAS28 <2.6) were included in this study. The study was approved by the Ethics Committee of the Hallym University Sacred Heart Hospital. Medical records were reviewed for information pertaining to age, sex, disease duration, and treatment duration. Joint assessment comprised the numbers of tender and swollen joints of the 28 joints included in DAS28 plus the ankle and ten MTP joints. Joint assessment was performed by a rheumatologist with 16 years of experience in performing joint examinations. Additionally, data were collected on C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), rheumatoid factor (RF), anti-citrullinated protein antibody (ACPA), patients' global assessments of disease activity using 100-mm visual analog scales, and prescription records for DMARDs, biologic agents, and glucocorticoids. The presence of bone erosions in the foot x-ray at the time of remission was noted. All data are presented as means ± standard deviations.

Table I. Characteristics of the patients (n=147).

Variable	n. (%)
Age (years)	50.8± 12.5
Female	110 (74.8)
Mean number of remission episode (median, range)	1.44 (1,1-4)
Disease duration (months)	41.6± 40.7
RF positive	76 (51.7)
RF titer (IU/mL)	134.0± 178.4
ACPA positive	52 (35.4)
ACPA titer (AU/mL)	152.0± 110.4
Baseline ESR (mm/hr)	25.0± 26.0
Baseline CRP (mg/L)	14.4± 26.6

RF: Rheumatoid factor; ACPA: Anti-citrullinated protein antibody; baseline ESR: Erythrocyte sedimentation rate at the start of treatment; baseline CRP: C-reactive protein at the start of treatment. Data are expressed as mean±standard deviation, unless specified otherwise.

Table II. Clinical profile of DAS28 remission (Total number of remission episodes = 213).

Variable	
DAS28 (range)	1.84 ± 0.57 (0.14–2.59)
Swollen joint count in 28 joint (range)	0.4 ± 0.9 (0–6)
Tender joint count in 28 joint (range)	1.5 ± 2.3 (0–13)
Patient global assessment of disease activity	27.8 ± 18.8
ESR (mm/hr)	5.9 ± 5.5
CRP (mg/L)	1.1 ± 2.9
Ankle/foot swollen joint count (range)	0.3 ± 0.9 (0–8)
Ankle/foot tender joint count (range)	0.9 ± 1.7 (0–9)
Any ankle/foot joint swelling (%)	25 (11.7)
Isolated ankle/foot joint swelling (%)	15 (7)
Any ankle/foot joint tenderness (%)	81 (38.0)
Isolated ankle/foot joint tenderness (%)	19 (8.9)

DAS28: 28 joint disease activity score; ESR: erythrocyte sedimentation rate; isolated ankle/foot swelling or tenderness: the presence of swelling/tenderness in ankle/foot joint without involvement of 28 joints included in DAS28. Data are expressed as mean ± standard deviation, unless specified otherwise.

Results

In total, 213 episodes of DAS28 remission in 147 patients were included. The mean age of the included patients was 51 years, and 74.8% were female. The mean duration of disease was 41.6±40.7 months. The characteristics of the patients are shown in Table I. At the time of remission, patients were being treated with methotrexate (55.8%), hydroxychloroquine (42.9%), leflunomide (15.6%), or a biologic agent (etanercept, n=5; adalimumab, n=1; infliximab, n=1; tocilizumab, n=4; golimumab, n=1; abatacept, n=1) (8.8%). The mean duration of treatment was 31.5±26.4 months. Prednisolone was administered to 74.8% of the patients at a mean daily dosage of 3.1 mg.

At the time of remission, the mean DAS28 value of the patients was 1.84 (range, 0.14–2.59). The mean swollen and tender joint counts for the 28 joints at the time of remission were 0.4 (range, 0–6) and 1.5 (range, 0–13), respectively. The clinical profiles of the patients at the time of DAS28 remission are shown in Table II. Overall, 11.7% and 38% of the patients in clinical remission had foot MTP/ankle swollen joints and tender joints, respectively (mean swollen and tender joint counts: 0.3 [range, 0–8] and 0.9 [range, 0–9]). Moreover, 7.0% and 8.9% of the patients in clinical remission had foot MTP/ankle swollen joints (mean, 1.9; range, 1–5) and tender joints (mean, 2.6; range, 1–9) without involvement of any of the 28 joints included in DAS28. Sixty-nine of the 147 patients in remission were evaluated using foot A–P radiography at the time of remission, and erosive changes in the MTP joints were found in 20 patients (29%). Of these 20 patients, five (25%) had new erosions that were absent at the time of RA diagnosis.

Discussion

As tight control of disease activity and the achievement of clinical remission are gaining importance for the management of RA, various definitions of disease activity have been proposed, including the ACR criteria, DAS, DAS28, simplified disease activity index (SDAI), and clinical disease activity index (CDAI). Among these, DAS28 is used frequently owing to its simplicity and relative ease of application. In the present study, many of the RA patients with clinical remission based on DAS28 were found to have residual joint activity, including ankle/foot joint involvement.

The original DAS criteria included the Richie articular index of tender joints, 44 swollen joint counts, ESR, and the patient's general health on VAS, whereas the DAS28 system limited the joint count to 28, omitting the ankle, foot MTP, and foot PIP joints (24). Although DAS <1.6 has been reported to correlate well with the ACR remission criteria, and DAS28 <2.6 correlates with DAS <1.6 (19,25,26), the implications of omitting the foot and ankle joints in deriving DAS28 are not well understood. Landewe *et al*. (22) have proposed that DAS remission and DAS28 remission may disguise different situations with respect to disease activity as a consequence of the activities in joints that are not included in the reduced joint count. In one cohort study, 29% of patients in remission based on DAS28 <2.6 had at least one painful MTP joint, and 31% had at least one swollen MTP joint during a maximum of 8 years of follow-up (27). A recent study examined patients with early RA by categorising them into three 'regional radiographic damage progression' groups: predominant progression in the foot; similar progression in the hand and foot; and predominant progression in the hand. In that study, DAS28 underestimated disease activity in the "predominant progression in the foot" group. In this group, joint counts for the feet were related to radiographic progression (28). However, recent reports show that DAS28 correlates well with the disease activity index, including MTP or ankle joints. Kapral *et al*. (29) compared the disease activities of the 28-joint with those of the 32-joint counts, which included the ankle and combined foot MTP joints, and found out that the frequency of remission did not change when the 28-joint count was replaced by a 32-joint count in the composite indices. Patients with foot involvement often had DAS28 >2.6 because these patients already had other findings that raised the DAS28. A recent study compared the rate of remission, progression of radiographic findings, and health assessment questionnaire (HAQ) using the 38-joint count in 10 MTP joints and a 28-joint count in 421 patients with early RA (30). Of the patients who achieved remission at 1 year according to the 28-joint count, 26% to 40% showed disease activity in the feet. However, misclassification due to reduced joint count was observed in only 2–3% of cases. Furthermore, a state of remission defined by both the 38-joint count and 28-joint count increased the likelihood of stability in the radiograph and HAQ with similar likelihood ratios.

In the present study, a significant number of patients in clinical remission, as defined by DAS28 <2.6, had foot MTP and ankle involvement, with some patients even showing isolated ankle or MTP joint involvement without evidence of disease activity in other joints, which is in line with a previous report (28). Among those who had radiographs available for examination, 29% showed radiographic MTP joint erosions at the time of clinical remission, and 7% had progression of erosion since the time of diagnosis. Although a very well-designed recent study has suggested that the inclusion of ankles and forefeet in the assessment of remission is not required, that study also showed that a significant number of patients in remission had residual activity in the feet (26% by the Boolean definition and 36% by the SDAI definition) (30). Additionally, the authors noted that a low number of patients reaching remission warrants caution in the interpretation of radiologic progression in the hands and feet separately.

In the present study, we examined many RA patients in clinical remission, as defined by DAS28 <2.6. This is the first report describing the clinical profiles of Asian patients with RA in remission and the extent of foot/ankle joint involvement in these patients. Nevertheless, this study has limitations. First, the patients were from a single center. Second, the included patients had variable disease duration at the time of data analysis, and the baseline DAS28 value was not available for a significant number of patients. Third, the involvement of foot proximal interphalangeal joints (PIP) was not assessed, which limits the full implication of foot joint involvement. Fourth, formal radiographic scoring was not performed, and radiologic damage was only assessed as the presence or absence of erosions in the MTP joints.

Our results show that patients with RA and DAS28 remission frequently have residual disease activity in the ankle and foot joints. This means that although many scoring systems for defining disease activity are available, composite indices are only part of what a rheumatologist does, and there is no cookbook medicine where the score is the only guideline dictating therapy. Since disease activity of the forefeet can lead to joint damage, pain, and disability in weight-bearing activities (31), inclusion of these joints in the clinical examination is necessary.

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