Positive synovial vascularity in patients with low disease activity indicates smouldering inflammation leading to joint damage in rheumatoid arthritis: time-integrated joint inflammation estimated by synovial vascularity in each finger joint

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Abstract

Objective. To investigate the relationship between synovial vascularity and joint damage progression in each finger joint of patients with RA under low disease activity during treatment with biologic agents.

Methods. We studied 310 MCP and 310 PIP joints of 31 patients with active RA who were administered adalimumab (ADA) or tocilizumab (TCZ). Patients were examined with clinical and laboratory assessments. Power Doppler sonography was performed at baseline and at weeks 8, 20 and 40. Synovial vascularity was evaluated according to quantitative measurement. Hand and foot radiography was performed at baseline and at week 50.

Results. Composite scores of the DAS with 28 joints and the Simplified Disease Activity Index (SDAI) were significantly decreased from baseline to week 8, being sustained at a low level by biologic agents during the observational period. MCP and PIP joints with positive synovial vascularity after week 8 showed more subsequent joint damage progression than joints without synovial vascularity throughout the follow-up. The changes in radiographic progression in these joints were independent of the sum of synovial vascularity from baseline to week 40 or the occasional occurrence of positive synovial vascularity.

Conclusion. Smouldering inflammation reflected by positive synovial vascularity under low disease activity was linked to joint damage. The damage progressed irrespective of the severity of positive synovial vascularity. Even with a favourable overall therapeutic response, monitoring of synovial vascularity has the potential to provide useful joint information to tailor treatment strategies.

Trial registration. University Hospital Medical Information Network Clinical Trials Registry; http://www.umin.ac.jp/ctr/; UMIN000004476.

Key words: rheumatoid arthritis, power Doppler sonography, synovial vascularity, low disease activity.

Introduction

In RA, clinical evaluations for disease activity such as patients’ symptoms, joint examinations and laboratory data do not have enough power to provide details on local joint inflammation [1]. To assess rheumatoid disease activity, composite scores such as the ACR core data set or the DAS with 28 joints (DAS28) have been developed to
compensate for the weak points in the use of a single clinical marker [2, 3]. Although these composite scores have been well established as disease activity markers, they cannot precisely predict the destruction of individual joints.

The appearance and increase in synovial vascularity related to vasodilation and angiogenesis indicates active joint inflammation [4]. Power Doppler sonography (PDS) enables visualization of synovial vascularity and numerical representation of local inflammation [5, 6].

We focused on the clinical significance of synovial vascularity in RA. We previously reported the prediction of the progression of local finger joint damage via early changes in synovial vascularity [7, 8]. Interestingly, we observed finger joints with persistence of synovial vascularity after achieving low disease activity. Here we report on the relationship between synovial vascularity and joint damage progression in two patient groups treated with different biologic agents, focusing on finger joints with positive synovial vascularity after achieving low disease activity.

Patients and methods

Patients

Thirty-one patients with RA who had started adalimumab (ADA) or tocilizumab (TCZ) therapies were analysed. The patients had been pre-treated with DMARDs [ADA: eight patients with MTX, one with tacrolimus (TAC), one with bucillamine (BUC) and one with MTX + TAC; TCZ: nine patients with MTX, one with BUC and two with TAC] or pre-treated with biologic agents [ADA: one patient with MTX + infliximab (IFX); TCZ: three patients with MTX + IFX, one with MTX + etanercept and two with MTX + ADA]. Despite these treatment histories, all patients were refractory cases having at least one swollen joint in the MCP/PIP joints and a DAS28-ESR > 3.2. Demographic, clinical and laboratory characteristics of the patients are shown in Table 1. After baseline examinations, ADA was given to 13 patients and TCZ to 18 patients. The biologic agents were given according to the standard protocols (ADA 40 mg s.c. injection bi-weekly, TCZ 8 mg/kg i.v. infusion every 4 weeks). This study was conducted in accordance with the Declaration of Helsinki and was approved by the local ethics committee of Hokkaido Medical Center for Rheumatic Diseases. Informed consent was obtained from all patients before they entered the study.

Clinical examination

Swollen and tender joints and global assessment on a visual analogue scale (VAS) were assessed at baseline and at weeks 8, 20 and 40 by rheumatologists (J.F., M.S., M.M., K.T.) who were blinded to the ultrasonographic results. Blood tests for ESR and CRP were performed at each assessment.

Ultrasonography and assessment

Ultrasonography was performed at baseline and at weeks 8, 20 and 40 by one of three US experts (M.H., F.S., A.N.) specialized in musculoskeletal ultrasonography who were blinded to other clinical information. A linear array transducer (13 MHz) and ultrasonographic machine were used (EUP-L34P, EUB-7500, Hitachi, Tokyo, Japan). Power Doppler settings have been previously described [7, 8]. First to fifth MCP and first to fifth PIP joints were scanned in the longitudinal plane over the dorsal surface. The quantitative PDS method was established in a previous report [8]. A value of synovial vascularity was determined by counting the number of vascular flow pixels in the region of interest.

Radiography and assessment

Plain radiographs of hands, wrists and feet were obtained at baseline and at week 50. Radiological assessments were examined according to the Genant-modified Sharp score (GSS) by a rheumatologist (M.S.) who was blinded to other clinical information [9].

Statistical analysis

Differences of composite parameters were examined using the Student’s t-test and other data were examined using a non-parametric test (Wilcoxon’s signed-rank test and Mann–Whitney U test). Intra- and interobserver reliability of quantitative PDS were estimated by intraclass correlation coefficients (ICCs). The smallest detectable change for the radiographic score change was calculated according to a previous study [10]. P < 0.05 indicated statistical significance. Statistical analyses were calculated with the use of Excel (Microsoft, Redmond, WA, USA) and MedCalc 12.1.4.0 (MedCalc Software, Mariakerke, Belgium).

Results

Clinical disease activity

At baseline there were no significant differences of DAS28-ESR and SDAI between the ADA and TCZ groups (Table 1). In both groups these parameters were significantly decreased from baseline to week 8, followed by sustained low disease activity (ADA: P = 0.0007, P = 0.0005; TCZ: P < 0.0001, P < 0.0001, respectively) (Table 1).

Radiographic evaluation of joint damage

At baseline there were no significant differences in total GSS (TGSS) between the ADA and TCZ groups (Table 1). In both groups the TGSS increased significantly from baseline to week 50 (P = 0.0122, P = 0.0181, respectively).

Local GSS (LGSS) was evaluated in each finger joint. In the ADA group the median of the LGSS at baseline for MCP and PIP joints was 2 (interquartile range (IQR) 2–4) and 3 (IQR 1.5–4), respectively, and in the TCZ group the median of the LGSS at baseline for MCP and PIP joints was 3 (IQR 2–4) and 3 (IQR 2–4), respectively. The smallest detectable change values was calculated for the LGSS for single MCP and PIP joints [0.33, 0.31 less than the smallest unit of GSS scoring (0.5)].
TABLE 1 Clinical and laboratory characteristics of patients at baseline

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<th>ADA</th>
<th>TCZ</th>
<th>P-value</th>
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<tr>
<td>Age, mean (range), years</td>
<td>53 (24–78)</td>
<td>56.4 (33–77)</td>
<td>0.516</td>
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<tr>
<td>Sex, female/male, n</td>
<td>12/1</td>
<td>18/1</td>
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<tr>
<td>Duration of symptoms, median (IQR), months</td>
<td>62 (11–147)</td>
<td>142 (72–178)</td>
<td>0.156</td>
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<td>ESR, median (IQR), mm/h</td>
<td>48 (34–54)</td>
<td>54 (34–64)</td>
<td>0.399</td>
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<tr>
<td>CRP, median (IQR), mg/dl</td>
<td>0.51 (0.09–0.89)</td>
<td>1.31 (0.24–3.03)</td>
<td>0.089</td>
</tr>
<tr>
<td>Swollen joint count, median (IQR)</td>
<td>3 (2–5)</td>
<td>5 (3–7)</td>
<td>0.179</td>
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<tr>
<td>Tender joint count, median (IQR)</td>
<td>5 (1–8)</td>
<td>4 (2–9)</td>
<td>0.984</td>
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<td>Patient’s global assessment by VAS, median (IQR)</td>
<td>50 (42–65)</td>
<td>67 (40–80)</td>
<td>0.544</td>
</tr>
<tr>
<td>Examiners global assessment by VAS, median (IQR)</td>
<td>40 (40–50)</td>
<td>50 (33–70)</td>
<td>0.56</td>
</tr>
<tr>
<td>DAS28-ESR (s.d.)</td>
<td></td>
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<td>Baseline</td>
<td>5.03 (1.16)</td>
<td>5.28 (1.08)</td>
<td>0.575</td>
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<td>Week 8</td>
<td>2.96 (0.86)</td>
<td>2.93 (0.81)</td>
<td>0.936</td>
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<td>SDAI (s.d.)</td>
<td></td>
<td></td>
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<tr>
<td>Baseline</td>
<td>21 (10.5)</td>
<td>24.7 (11.3)</td>
<td>0.275</td>
</tr>
<tr>
<td>Week 8</td>
<td>7.61 (5.48)</td>
<td>8.84 (4.31)</td>
<td>0.60</td>
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<td>TGSS, median (IQR)</td>
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<tr>
<td>Baseline</td>
<td>99.5 (73–116)</td>
<td>122.75 (98.75–160.75)</td>
<td>0.238</td>
</tr>
<tr>
<td>Week 50</td>
<td>108.5 (73–134.5)</td>
<td>125 (99.88–164.88)</td>
<td>0.271</td>
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Relationship between positive synovial vascularity and radiographic progression in finger joints

In the ADA group the mean and median of local synovial vascularity at baseline for the MCP and PIP joints were 197 and 0 (range 0–3053) and 218 and 0 (range 0–2414), respectively. In the TCZ group the mean and median of local synovial vascularity at baseline for the MCP and PIP joints were 416 and 0 (range 0–4686) and 167 and 0 (range 0–3195), respectively. Local synovial vascularity in both the ADA and TCZ groups decreased significantly from baseline to week 8 (ADA: MCP P = 0.0001, PIP P < 0.0001; TCZ: MCP P = 0.0002, PIP P = 0.004). We next categorized finger joints into four groups according to the occurrence of patterns of positive synovial vascularity: joints without synovial vascularity throughout the observational period [the negative (N) group], joints with positive synovial vascularity limited to the period from the baseline to week 8 [the therapeutic response (R) group], joints with intermittent occurrence of positive synovial vascularity in the observational period [the intermittently positive (IP) group] and joints with persistent positive synovial vascularity throughout the observational period [the persistently positive (PP) group]. Each patient had a different pattern of joints with positive synovial vascularity: patients in the N group (ADA n = 2, TCZ n = 2), patients in the R group (ADA n = 3, TCZ n = 3), patients in the IP or PP groups (ADA n = 3, TCZ n = 6) and patients in the mixed R and IP or PP groups (ADA n = 5, TCZ n = 7).

The change in the LGSS (ΔLGSS) of the R group showed no progression as compared with the N group or showed improvement of joint damage in the PIP joints of the ADA treatment group (Fig. 1). We next focused on the joints with positive synovial vascularity after week 8, comprising the IP and PP groups. These joints showed an increased ΔLGSS as compared with the N group (Fig. 1). The ΔLGSS between the IP and PP groups showed no significant difference with either ADA or TCZ treatment (Fig. 1).

To analyse the relationship between synovial vascularity and ΔLGSS in more detail in the joints comprising the IP and PP groups, we calculated the sum of synovial vascularity of each finger joint from baseline to week 40 to represent the total exposure to inflammation during the treatment period. The medians of the sum of synovial vascularity with ADA therapy for the MCP and PIP joints were 1456 (range 71–6352) and 1136 (range 71–4757), respectively. The medians of the sum of synovial vascularity with TCZ therapy for the MCP and PIP joints were 2947 (range 71–11289) and 1385 (range 71–5964), respectively. We categorized these joints into two groups: those with a sum of synovial vascularity ≤ median value [the low-level (L) group], and those with a sum of synovial vascularity > median value [the high-level (H) group]. There were no significant differences in the ΔLGSS between the L group and H group with either ADA or TCZ treatment (Fig. 1).

Intra- and interobserver reliability for power Doppler ultrasonography

Representative PDS images for 20 MCP and 20 PIP joints were randomly chosen, and synovial vascularity was measured three times each by the three ultrasonographers (M.H., F.S. and A.N.). The obtained intraobserver ICC values were 0.997–0.999 for MCP joints and 0.998–0.999 for PIP joints. The interobserver ICC values were 0.992–0.996 for MCP joints and 0.991–0.999 for PIP joints.

Discussion

Our study revealed two noteworthy results. First, this study further emphasized a previous report [7] that early improvement and then disappearance of synovial vascularity resulted in reducing joint damage progression.
For ADA treatment, $\Delta$LGSS of MCP (A) and PIP joints (B) is shown. For TCZ treatment, $\Delta$LGSS of MCP (C) and PIP joints (D) is shown. Graphs on the left side show $\Delta$LGSS of the N, R, IP and PP groups (Results section), which were categorized according to the occasional occurrence of positive synovial vascularity. For each joint in the IP and PP groups, the sum of synovial vascularity from baseline to week 40 was calculated and then categorized as L and H groups (Results section). Graphs on the right side show $\Delta$LGSS of the L and H groups.
Secondly, a novel result was that persistence of positive synovial vascularity in local finger joints showed joint damage progression despite achieving low disease activity by biologic therapies. Interestingly, the ΔLGSS progressed independently of time-integrated joint inflammation estimated by the sum of synovial vascularity or occasional occurrence of positive synovial vascularity. These joints indicate the presence of low-level local joint inflammation, i.e. smouldering inflammation. The smouldering inflammatory joints could be categorized as a variation of subclinical synovitis described below.

Analysis of RA in the clinical remission phase revealed that there were asymptomatic or symptom-limited joints with poor prognosis. This joint inflammation or so-called subclinical synovitis can only be detected with imaging techniques [11–14]. The growing importance of imaging remission of rheumatoid activity has been confirmed, and imaging techniques such as joint ultrasonography have focused on detailed detection of local joint inflammation [15, 16].

Synovial vascularity detected by PDS is irrefutably linked to the level of joint inflammation [17, 18]. Naredo et al. [19] reported the correlation between time-integrated values of joint counts for positive synovial vascularity and total joint damage progression at 1 year. From these results, we speculated that increasing and persistent synovial vascularity might result in advanced joint damage progression; hence an increase in the occasional occurrence of positive synovial vascularity or the sum of synovial vascularity worsens the structural damage in smouldering inflammatory joints. Our data revealed that joints with positive synovial vascularity after week 8 (IP and PP groups) showed joint damage progression; however, their ΔLGSS progression did not relate to the occasional occurrence of positive synovial vascularity or the sum of synovial vascularity (Fig. 1). Accordingly, we concluded that the structural damage in joints with smouldering inflammation progressed independently of the level of the sum of synovial vascularity or the occasional occurrence of positive synovial vascularity. Importantly, the result might indicate that even low levels of positive synovial vascularity that occurred only once during the clinical improvement phase showed a risk for structural damage.

Although a correlation between the progression of systemic joint damage and time-integrated values of joint counts for positive synovial vascularity was reported [19], our study, which focused on synovitis and joint damage in individual finger joints, did not show such correlation. Whereas the previous study [19] showed the effect of non-biologic DMARDs, we studied biologic agents that rapidly improved acute inflammation. The DMARDs have slow therapeutic effect; thus the relationship between exposure to inflammation and joint damage progression may be closer in non-biologic DMARD users. Further, our data showed that some patients were in the mixed R and IP or PP group after starting biologic agents. This might indicate a discrepancy between overall therapeutic response and local joint response. Limitations of our study were its small scale and short observation period. Further larger studies are needed to confirm our observations.

In RA, tight control of joint inflammation is necessary for better outcomes. Treatment strategies should be changed according to the clinical response. Monitoring of synovial vascularity has the potential to provide useful joint information for daily practice and to tailor treatment strategies in RA.

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<th>Rheumatology key messages</th>
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<tr>
<td>• Finger joints with positive synovial vascularity under low disease activity showed structural deterioration in RA.</td>
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<tr>
<td>• Monitoring of synovial vascularity has the potential to provide useful information for daily practice in RA.</td>
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Disclosure statement: The authors have declared no conflicts of interest.

References


