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Concise report

Rheumatoid arthritis patients with predominantly tender joints rarely achieve clinical remission despite being in ultrasound remission

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Abstract

Objectives. Given that subjective variables might reduce remission by composite DAS (CDAS), the main objectives were to explore whether RA patients with mainly tender *vs* mainly swollen joints had differences in patient-reported outcome measures (PROMs), clinical or US assessments or in achieving remission defined by CDAS or US.

Methods. In a Nordic multicentre study, RA patients initiating tocilizumab were assessed by PROMs, clinical, laboratory and US assessments (36 joints and 4 tendons) at baseline, 4, 12 and 24 weeks. Remission was defined according to clinical disease activity index (CDAI)/Boolean or no Doppler activity present. Tender–swollen joint differences (TSJDs) were calculated. Statistics exploring changes over time/differences between groups included Wilcoxon, Mann–Whitney, Kruskal–Wallis and Spearman tests.

Results. One hundred and ten patients were included [mean (S.D.) age 55.6 (12.1) years, RA duration 8.7 (9.5) years]. All PROMs, clinical, laboratory and US scores decreased during follow-up ($P < 0.001$). During follow-up, tender joint counts were correlated primarily with PROMs [$r = 0.24$–0.56 ($P < 0.05$–0.001)] and swollen joint counts with US synovitis scores [$r = 0.33$–0.72 ($P < 0.05$–0.001)]. At 24 weeks, patients with TSJD > 0 had higher PROMs and CDAI ($P < 0.05$–0.001) but lower US synovitis scores ($P < 0.05$). Remission by CDAI/Boolean was seen in 26–34% and by Doppler 53%, but only 2–3% of patients with TSJD > 0 achieved CDAI/Boolean remission.

Conclusion. Patients with more tender than swollen joints scored higher on subjective assessments but had less US synovitis. They seldom achieved CDAS remission despite many being in Doppler remission. If patients with predominantly tender joints do not reach CDAS remission, objective assessments of inflammation should be performed.

Trial registration ClinicalTrials.gov, https://clinicaltrials.gov/, NCT02046616.

Key words: rheumatoid arthritis, biological treatment, ultrasound, patient-reported outcomes

CLINICAL SCIENCE

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Key messages

- Tender joint counts were primarily associated with patient-reported outcomes and swollen joint counts with US synovitis scores.
- RA patients with primarily tender joints seldom achieved clinical disease activity index/Boolean remission despite US remission.
- Objective assessments of inflammation are advocated in patients with more tender than swollen joints.

Introduction

In patients with RA, tender and swollen joint counts are included in most of the composite DASs (CDAS), including the clinical disease activity index (CDAI) [1] and the ACR/EULAR Boolean definition of remission [2]. Tender joints are part of the routine clinical examination, although there are several reasons for joint tenderness other than inflammation. In addition, even if there is a standardized examination technique regarding the amount of pressure to be applied to the joint for assessing tenderness [3], there is no consensus on where the pressure should be applied at the different joints, which might be a cause for only moderate reliability of the assessments [4]. In contrast, swollen joint assessment has a high face validity and is a cornerstone in the clinical evaluation of joint inflammation in patients with RA. Furthermore, swollen joints have been found to be highly associated with disease evaluation by assessors and US synovitis in RA patients [5].

RA patients with more tender than swollen joints have demonstrated higher levels of patient-reported outcome measures (PROMs) and are less likely to achieve CDAS and ACR/EULAR Boolean remission [7, 8]. So far, only one study on this topic has included US assessments, and in this single-centre study it was shown that the degree of US synovitis was lower in patients with predominantly tender compared with swollen joints [7]. CDAS remission is the primary goal when treating RA patients with biological treatment, hence factors that might impact the achievement of CDAS remission in patients with more tender than swollen joints should be explored further.

The present study is based on a 24-week Nordic multicentre study of RA patients who were examined by US during treatment with s.c. tocilizumab [9]. Tocilizumab is an IL-6 inhibitor that causes rapid reduction of CRP and ESR [6]. Thus, CDAI is usually the choice of CDAS when IL-6 inhibitors are used.

The present objectives were to examine the associations between tender or swollen joint counts and several clinical variables, to explore the differences in PROMs, clinical examinations and US assessments between patients with mainly tender *vs* mainly swollen joints and to investigate whether having predominantly tender joints influenced the achievement of remission defined by CDAI, ACR/EULAR Boolean or US examinations.

Methods

Patients ($\geq$18 years old) with active RA according to the revised (1987) ACR [10] or EULAR/ACR (2010) criteria [11] (moderate to severe RA with DAS28-ESR $>$ 3.2) and with inadequate response or intolerance to conventional synthetic DMARDs (csDMARDs) were included [9]. Inclusion and exclusion criteria were as previously described [9, 12]. The present study includes only the subgroup of patients from the main study (TOZURA) [12] who were assessed by US [9]. All PROMs, clinical, laboratory and US examinations were performed at baseline and after 4, 12 and 24 weeks [9].

Protocols, amendments and informed consent documentation of the studies were approved by the respective local independent ethics committees (Norwegian ethical committee 2013/1857/REK South-East; Clinical trial identifier: NCT02046616). All patients provided written, informed consent according to the Declaration of Helsinki.

Patient-reported outcome measures (PROMs)

We focused on the most common PROMs in RA; the patient global assessment of disease activity (PGA) and joint pain on visual analog scales (VAS, 0–100), in addition to the Health assessment questionnaire-disability index (HAQ-DI) [13].

Clinical and laboratory assessments

The 28-joint assessments for tender/swollen joint counts (TJC/SJC) were performed by rheumatologists or trained study nurses depending on the study site, and examinator's global assessments were scored by VAS (0–100). ESR was examined locally at each hospital laboratory, whereas serum was sent to a central study laboratory for examination of CRP. CDAI remission ($\leq$2.8) [1] and ACR/EULAR Boolean remission [2] were calculated at 12 and 24 weeks.

US examination

The US examinations included grey scale (GS) and power or colour Doppler scored semi-quantitatively on a four-point scale (0 = no, 1 = minor, 2 = moderate, 3 = major presence of GS or Doppler) of 36 joints [wrists (radiocarpal, midcarpal and radioulnar joints assessed separately), MCP 1–5, PIP 2–3, elbow, knee, tibiotalar and MTP 1–5, in addition to the extensor carpi ulnaris

and tibialis posterior tendons] according to the Norwegian US atlas [9, 14]. The 39 ultrasonographers were blinded to the PROMs, clinical assessments and laboratory markers of the patients during the entire study. The intra-rater reliability for the ultrasonographers at the involved centres was explored, and median (range) intraclass correlation coefficient was 0.89 (0.79–0.96) [9]. US sum scores were calculated separately for GS and Doppler, and the scores included all joints and tendons. Doppler remission was defined as a sum score Doppler of zero.

Statistical methods

The patients were divided into two groups with either less than or equal to median TJC or more than median TJC at each visit. Differences in PROMs, clinical, laboratory and US assessments between the two groups were explored by Mann–Whitney *U*-test. The tender–swollen joint difference (TSJD) was calculated for each examination, and patients with predominantly tender joints (TSJD >0) were compared with patients with predominantly swollen joints (TSJD ≤ 0). The data did not have a normal distribution, and non-parametric tests were used. Associations were explored by Spearman's rank correlations, differences between patients TSJD >0 *vs* TSJD ≤ 0 by Mann–Whitney *U*-test, and changes from baseline by use of the Wilcoxon signed rank test. The TSJDs were divided in quartiles at baseline, with one group including all patients with TSJD ≤ 0 and the rest divided into three groups with increasing TSJD. During follow-up, the percentage of patients with TSJD ≤ 0 increased, but similar grouping definitions to those used at baseline were applied during follow-up when looking at differences between the quartiles by use of the Kruskal–Wallis test. Significance was defined as $P < 0.05$, and all calculations were performed by use of SPSS Statistics v.21.

Results

A total of 110 patients [mean (S.D.) age 55.6 (12.1) years and RA duration 8.7 (9.5) years, 83% female and 81% anti-CCP positive] were examined [9]. Only patients continuing s.c. tocilizumab were included in the present calculations (4 weeks, $n = 102$; 12 weeks, $n = 95$; 24 weeks, $n = 91$). PROMs, examinator's global assessments, laboratory variables and US scores decreased significantly from baseline to 24 weeks for all patients ($P < 0.001$; Table 1) and when patients with TSJD >0 or TSJD ≤ 0 were tested separately ($P \leq 0.05$). Patients with higher *vs* lower than the median TJC had no significant differences in US or laboratory assessments at any visit, but patients with higher than median TJC had higher joint pain at all visits ($P < 0.001$–0.013), in addition to higher PGA, examinator's global assessments and HAQ-DI at three of the visits ($P < 0.001$–0.008) and no significant difference at one visit.

Correlations during follow-up

At the 4-, 12- and 24-week visits, TJC was significantly correlated with the PROMs ($P < 0.05$–0.001), with correlation coefficients (r) in the range of 0.38–0.49 for PGA, 0.33–0.56 for joint pain and 0.28–0.36 for HAQ-DI. However, the correlations with GS/Doppler US scores were 0.06–0.18 (not significant). SJC had no significant correlations with any of the PROMs ($r = 0.01$–0.16) but was significantly correlated with GS/Doppler US scores ($r = 0.33$–0.72; $P < 0.05$–0.001).

Associations within the TSJD groups

Table 1 shows separate follow-up results for patients with TSJD >0 or TSJD ≤ 0. Compared with the TSJD ≤ 0 group, patients with TSJD >0 had significantly higher levels of PROMs, whereas they had lower GS and Doppler US scores.

Associations between quartiles of TSJD

At 4-, 12- and 24-week follow-up visits, there were significantly higher PROMs and CDAI with increasing TSJD ($P = 0.036$ to <0.001), whereas this was not the case for sum scores GS or Doppler.

Achievement of remission depending on levels of TSJD

The percentages of patients reaching CDAI, ACR/EULAR Boolean or Doppler remission are shown in Table 2. No patients with TSJD >0 reached CDAI or ACR/Boolean remission at 12 weeks, whereas 24% of these patients were in Doppler remission. At 24 weeks, only 2–3% of patients with TSJD >0 were in CDAI or ACR/EULAR Boolean remission, whereas 26% of these patients were in Doppler remission. Subgroup analyses showed that no patients with TSJD ≥ 2 reached CDAI or ACR/Boolean remission.

Of the patients with TSJD >0 and not reaching ACR/Boolean remission at 24 weeks ($n = 35$), 77% had TJC >1 and 86% had PGA >10 (of 0–100), whereas only 14% had SJC >1 and none had CRP >1 mg/dl. Of those patients with TSJD ≤ 0 who had not achieved ACR/EULAR Boolean remission at 24 weeks, 63% had TJC >1, 34% had SJC >1, 34% had PGA >10 (of 0–100) and 6% had CRP >1mg/dl.

Discussion

We found TJC to be associated predominantly with high scores of PROMs, whereas SJC was associated with the US synovitis scores. Patients with a higher number of tender than swollen joints had higher scores for all recorded PROMs and CDAI, whereas they had lower US synovitis scores. Importantly, only a few patients with predominantly tender joints achieved CDAI or ACR/EULAR Boolean remission at 24 weeks, whereas most patients in ACR/EULAR Boolean remission had predominantly swollen joints. However, there were no

Table 1 Differences between patients with predominantly tender *vs* predominantly swollen joints during follow-up

	TSJD > 0/TSJD ≤ 0 at baseline, median (IQR)	TSJD > 0/TSJD ≤ 0 at 4 weeks, median (IQR)	TSJD > 0/TSJD ≤ 0 at 12 weeks, median (IQR)	TSJD > 0/TSJD ≤ 0 at 24 weeks, median (IQR)
Frequencies of patients with TSJD > 0/TSJD ≤ 0	64.0%/36.0%	57.8%/42.2%	58.4%/41.6%	38.5%/61.5%
Patient's global VAS	55 (35–70)/54 (36–70)	**35 (24–49)/20 (16–45)***	**25 (12–43)/11 (3–15)****	**26 (15–43)/8 (2–17)****
Joint pain VAS	60 (34–74)/54 (34–69)	**37 (20–53)/18 (10–47)***	**25 (11–39)/6 (2–13)****	**23 (13–41)/6 (1–12)****
HAQ-DI	1.25 (0.75–1.75)/ 1.25 (0.66–1.63)	**1.0 (0.63–1.50)/ 0.56 (0.13–1.16)***	**0.63 (0.25–1.25)/ 0.25 (0.00–1.00)***	**0.75 (0.19–1.38)/ 0.13 (0.00–0.88)***
CDAI	22.7 (17.7–29.9)/ 26.9 (16.0–32.1)	**16.5 (9.6–24.0)/ 8.4 (4.2–18.1)***	**8.5 (6.4–12.9)/ 3.7 (1.4–7.9)****	**6.9 (4.3–10.2)/ 2.8 (1.1–9.3)****
Examiner's global VAS	*30 (22–48)/42 (35–59)***	16 (11–29)/20 (12–32)	10 (5–18)/8 (4–18)	8 (4–11)/4 (1–11)
Sum score GS	*19 (12–28)/28 (18–49)**	*14 (7–25)/20 (12–34)**	12 (5–18)/15 (6–29)	*6 (2–11)/10 (4–23)**
Sum score Doppler	*5 (1–14)/13 (4–27)**	3 (0–8)/5 (2–7)	1 (0–4)/1 (0–5)	*0 (0–1)/1 (0–4)**
CRP (mg/l)	*4.4 (2.0–11.9)/8.0 (3.6–13.9)**	0.3 (0.2–0.5)/0.2 (0.2–0.4)	0.2 (0.2–0.6)/0.2 (0.2–0.6)	0.2 (0.2–0.3)/0.2 (0.2–0.4)
ESR (mm/h)	*18 (10–30)/28 (16–38)**	4 (2–5)/5 (2–9)	3 (2–5)/4 (2–5)	*2 (2–4)/4 (2–5)**
Tender joint count	**9 (6–13)/6 (2–10)****	**7 (4–11)/1 (0–4)****	**4 (3–6)/0 (0–1)****	**3 (1–6)/0 (0–1)****
Swollen joint count	*5 (2–7)/10 (4–14)****	2 (0–5)/3 (1–7)	0 (0–2)/1 (0–4)	*0 (0–1)/1 (0–3)**

Bold indicate significantly higher levels and italic lower levels of the variables for patients with TSJD > 0 *vs* TSJD ≤ 0. *$P < 0.05$, **$P \leq 0.001$.CDAI: clinical disease activity index; GS: grey scale US; HAQ-DI: Health assessment questionnaire-disability index; IQR: interquartile range; TSJD: tender–swollen joint difference; VAS: visual analog scale.

Table 2 Percentages of patients reaching clinical disease activity index, ACR/EULAR Boolean or Doppler remission at 12 and 24 weeks across levels of tender–swollen joint difference

Visit	Definition of remission	Total patients in remission, *n* (%)	TSJD ≤ 0, % in remission	TSJD > 0, % in remission	TSJD = 1, % in remission	TSJD ≥ 2, % in remission
12 weeks (*n* = 95)	CDAI remission	17 (17.9)	17.9	0.0	0.0	0.0
	Boolean remission	13 (13.7)	13.7	0.0	0.0	0.0
	Sum score Doppler = 0	40 (42.1)	17.9	24.2	4.2	20.0
24 weeks (*n* = 91)	CDAI remission	33 (36.3)	33.0	3.3	3.3	0.0
	Boolean remission	26 (28.6)	26.4	2.2	2.2	0.0
	Sum score Doppler = 0	48 (52.8)	26.4	26.4	11.0	15.4

CDAI: clinical disease activity index; TSJD: tender–swollen joint difference.

differences in the percentages reaching Doppler remission across TSJD groups.

Low correlations between TJC and US synovitis scores have been described previously [7, 8]. In addition, low correlations have been shown between PROMs and MRI synovitis in RA patients [15]. Our findings are supported by a recent study of established RA patients that found swollen but not tender joints to be associated with US synovitis [5].

We found patients with predominantly tender joints to have the highest PROM scores, in line with a previous study [7]. High TSJD has been found to indicate FM [16], which can cause higher scores of PROMs, resulting in increased CDAS levels. This has been shown to result in medical overtreatment [17].

In the present study, CDAI or ACR/EULAR Boolean remission was seldom achieved in patients with predominantly tender joints, although many of these

patients reached Doppler remission. As shown in other studies [7–9], there is a major discrepancy in the number of patients achieving remission depending on the different CDAS applied. Remission is the treatment goal, and the description of large discrepancies in achievement of remission between different CDAS assessments used in the same RA cohorts [9, 18] indicates that achieving remission might be dependent on the choice of CDAS. Given that the different anti-rheumatic medications exert their main effects on inflammation, further studies are needed to develop clinical composite scores that reflect the inflammatory activity more closely.

The present finding of a significant association between TJC and PROMs, but no association between TJC and objective assessments of inflammation, might be related to tenderness being caused by factors other than inflammation. Catastrophizing has been found to be a crucially important variable in understanding the experience of pain in patients with rheumatological disorders [19]. A recent study found pain catastrophizing to be strongly associated with patients' perception of disease activity, but not with clinical or US assessments of inflammation, and higher levels of pain catastrophizing were longitudinally associated with higher CDAS scores [20]. Similar findings were seen in a recent longitudinal study, in which patients with TSJD >0 *vs* TSJD ≤ 0 were found to have significantly higher levels of pain catastrophizing [7]. Thus, pain catastrophizing, although not examined in our study, might be a potential explanation for the relationship between TJC and PROMs.

Strengths of the present study include the high number of RA patients undergoing comprehensive clinical and US assessment using a validated scoring system in a real-life setting. A limitation is the high number of assessors. However, the patients were followed by the same clinical assessor and the same ultrasonographer, and the intra-reader consistency of examinations for US was found to be good. In addition, given that we found a major decrease of all the PROMs, clinical, laboratory and US assessments, this might suggest that a potential variation between the ultrasonographers had a low impact on our main results.

In conclusion, TJC had a low association with objective signs of inflammation, and patients with predominantly tender joints rarely reached composite score remission despite many achieving Doppler remission. Our study supports previous studies that question the specificity of tender joint assessment in the evaluation of inflammation in patients with established RA and highlight the importance of exploring whether non-inflammatory causes might explain the lack of achievement of CDAI or ACR/EULAR Boolean remission in patients with predominantly tender joints.

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Data availability statement

The data will be shared if there is a reasonable request for it.

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