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Swollen-tender ratio: a novel combination of routine measures to assess pain and treatment response in rheumatoid arthritis

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Pain is a hallmark symptom of rheumatoid arthritis (RA). Despite treatment with disease-modifying antirheumatic drugs (DMARDs), 71% of RA patients cite pain as a major priority (1), and approximately one-third of RA patients do not respond to DMARDs, according to the American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) response criteria (2). Studies report high rates of co-morbid fibromyalgia in RA (3), suggesting that a large subset of RA patients "centralize" their pain. These patients have widespread pain sensitivity, which may be due to alterations in central nervous system (CNS) pain regulatory mechanisms. It has been hypothesized that abnormalities in the CNS pain regulatory mechanisms predispose RA patients to poor DMARD response because DMARDs work on peripheral inflammatory pain mechanisms, rather than central pain mechanisms. In this issue of *Arthritis Care & Research*, Kristensen and colleagues (4) propose that the swollen-tender joint count ratio (STR), can identify RA patients with abnormal CNS pain regulatory mechanisms and that the STR predicts response to tumor necrosis factor (TNF) inhibitors.

Kristensen et al. characterized the STR in 2,507 RA patients starting TNF inhibitors in the South Swedish Arthritis Group Register. They also examined the association between baseline STR and DMARD response, assessed by the ACR 20% and 50% improvement criteria. STR was defined as the swollen joint count divided by the tender joint count, using the standard 28-joint assessment. Patients with no swollen and/or tender joints at baseline were excluded. Based on distribution plots, the STR was categorized into three groups: 1) low (STR < 0.5), 2) moderate (0.5 ≤ STR ≤ 1) and 3) high (STR > 1). At baseline, 14% had a STR in the low range, 47% had a STR in the moderate range, and 39% had a STR ratio in the high range. Patients with low STRs had higher pain levels than patients with moderate or high STRs, whereas patients with moderate/high STRs had higher C-reactive protein (CRP) levels and longer disease durations. After 6 months of anti-TNF treatment, patients with moderate/high baseline STRs (moderate STR: 39%, 95% CI 35-43%; high STR: 40%, 95% CI 36-44%) had significantly higher ACR50 response rates compared to those with low baseline STRs (23%, 95% CI 18-29%). In a multivariable logistic regression model adjusted for gender, disease duration, baseline disease activity score in 28 joints (DAS28), baseline

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Health Assessment Questionnaire (HAQ) score, corticosteroid use and methotrexate treatment, patients with moderate baseline STRs were significantly more likely to achieve an ACR50 response at 6 months, compared to patients with low baseline STRs (odds ratio 1.93, $P = 0.004$). Similarly, patients with high baseline STRs were significantly more likely to achieve an ACR50 response at 6 months than patients with low baseline STRs (odds ratio 2.82, $P < 0.001$).

Based on these data, the authors concluded that the STR is an important predictor of response to TNF inhibitors. The concept of the STR is attractive because it is easy to apply to routine clinical care. The components of the STR, the swollen and tender joint counts, are standard measures of RA disease activity, which are routinely obtained as a part of clinical assessments, and the STR ratio can be easily calculated during a clinical visit by simply dividing two numbers. It is particularly interesting that the association between STR and TNF response remained after adjustment for disease activity measures. These results suggest that the association between STR and TNF response was not simply an artifact of an association between inflammatory disease activity and treatment response. In fact, STR was a stronger predictor of TNF response than inflammatory measures of disease activity. CRP was not significantly associated with TNF response, and swollen joint count was only weakly associated with TNF response (OR 1.06, 95% CI 1.03-1.09).

The concept of the STR is novel. No other studies have employed the STR as a measure of either CNS pain mechanisms or a predictor of treatment response. As such, there are no data, beyond what is provided in this manuscript, regarding appropriate thresholds for low, moderate and high STRs. The authors examined distribution plots to determine the cut-off points. The largest number of patients had STRs between 0.5 and 1.0. Fourteen percent had STRs < 0.5, which is consistent with previous reports of the prevalence of fibromyalgia within the RA population (5, 6). This observation supports the face validity of the STR. However, additional studies are needed to determine whether these thresholds are appropriate when applied to other RA populations.

It is important to note that there is no consensus regarding the best method of assessing CNS pain mechanisms in RA (7). Although no studies have used the STR as a measure of these mechanisms, two previous studies used a similar measure, the difference between the tender and swollen joint count, to assess chronic widespread pain (5, 8). In these studies, a difference of ≥ 7 in the tender joint count minus the swollen joint count was used to define fibromyalgia. This measure was shown to be 72-83% sensitive and 80-98% specific compared to the gold standard for the diagnosis of fibromyalgia, defined by ≥ 11 tender points. Participants with joint count differences ≥ 7 had higher HAQ scores and higher depression scores than participants with joint count differences < 7, despite similar mechanical joint damage scores. Both of these studies were cross-sectional, and neither examined whether the difference in tender and swollen joint count could predict treatment response. However, the combination of data from these studies and the current study by Kristensen and colleagues suggests that the discrepancy between swollen and tender joint count may provide important information regarding pain mechanisms, beyond the information they separately provide about inflammatory disease activity.

A limitation of the current study is the absence of data showing a correlation between STRs and other measures of CNS pain mechanisms. The authors did not directly compare the STR among RA patients with known abnormalities in CNS pain regulatory mechanisms (e.g., patients with fibromyalgia versus those without fibromyalgia). They also did not examine correlations between the STR and quantitative sensory testing (evoked pain paradigms to assess experimental pain sensitivity), tender point examinations and survey measures. Other studies have shown that quantitative sensory testing methods, specifically pressure pain thresholds at the joints and conditioned pain modulation (a measure of the descending analgesic pain pathways), differ among RA patients compared to age and sex-matched controls (9). Future studies, examining how the STR performs compared to these measures will be important to determine the validity of the STR.

In summary, this study by Kristensen et al. presents a novel measure, the STR, which is comprised of two conventional methods of RA disease assessment, the swollen and tender joint counts. The authors conclude that the STR may be an important predictor of TNF response. These results clearly highlight the importance of physical examination, particularly the swollen and tender joint counts, in the assessment of RA patients. When deciding whether to start a TNF inhibitor, rheumatologists should assess whether patients have tenderness out-of-proportion to objective inflammatory measures. If pain, rather than inflammation, is the predominant feature, patients may not benefit from strong immunosuppressive agents. Additional studies are needed to determine whether the STR is a valid way of assessing CNS pain mechanisms in RA, and whether STR is independently associated with poor TNF response in other RA cohorts.

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