Declines of tender and swollen joint counts between 1985 and 2001 in patients with rheumatoid arthritis seen in standard care:

Possible considerations for revision of inclusion criteria for clinical trials

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ABSTRACT

Objective: To analyze tender and swollen joint counts in 3 cohorts of patients with rheumatoid arthritis (RA) seen in standard clinical care in 1985, 2000 and 2001, to compute the proportions of patients who had fewer than 6-12 tender or swollen joints, as possible evidence-based information toward more generalizable inclusion criteria for current and future RA clinical trials.

Methods: Tender and swollen joint counts were analyzed in 3 RA patient cohorts seen in Nashville, TN, USA: 125 seen in 1985, 152 in 2000, and 232 with early RA seen in a different setting in 2001.

Results: The median number of tender joints was 11 in 1985, versus 2 in 2000 and 4 in 2001, while the median number of swollen joints was 12 in 1985, versus 6 in 2000 and 5 in 2001. The number of tender joints among 28 assessed was ≥12, ≥6, ≥4, and ≥3 in 47%, 80%, 85% and 90% of patients in 1985, versus 20%, 37%, 44% and 49% in 2000, and 17%, 37%, 50% and 58% in 2001. The number of swollen joints among 28 assessed was ≥12, ≥6, ≥4, and ≥3 in 51%, 78%, 85% and 90% of patients in 1985, versus 20%, 50%, 64% and 67% in 2000, and 14%, 46%, 58% and 72% in 2001. More patients had ≥6 tender joints in 1985 (80%) than ≥3 tender joints in 2000 (49%) and 2001 (58%), or ≥6 swollen joints in 1985 (78%) than ≥3 swollen joints in 2000 (67%) and 2001 (72%).

Conclusion: Contemporary cohorts of patients seen in standard care have lower numbers of tender and swollen joints than in previous times. These findings might suggest consideration of revision of inclusion criteria for numbers of tender and swollen joints in contemporary RA clinical trials to improve generalizability.
INTRODUCTION

The joint count is the most specific clinical measure to quantify disease activity in patients with rheumatoid arthritis (RA). A tender and swollen joint count are included in the disease activity score (DAS) (1-3) and American College of Rheumatology (ACR) Core Data Set (4-6). Criteria for eligibility of patients to participate in RA clinical trials generally include 6-12 tender and 6-12 swollen joints (7;8).

We reported that the majority of consecutive patients in two cohorts of patients with RA seen in standard clinical care in Nashville, TN, USA, in 2000 and 2001 did not have 6 swollen or tender joints (7;8). Furthermore, the 2000 cohort appeared to have substantially more favorable clinical status than a cohort of patients seen in the same setting in 1985, the majority of whom did have 6 or more tender and swollen joints (9).

These observations suggested that 6-12 tender and swollen joints appeared to be appropriate inclusion criteria for RA clinical trials in past decades, but may be overly stringent at this time. Possible reduction in the number of tender and/or swollen joints required for inclusion might improve generalizability of contemporary and future RA clinical trials. However, relatively little published data are available concerning the specific number of tender or swollen joints, particularly fewer than 6, in patients outside of clinical trials, as formal joint counts are usually not performed by most rheumatologists in standard care (10). Therefore, in this report, we analyze the prevalence of 2-6 tender or swollen joints in patients in the 3 cohorts from standard care.
PATIENTS AND METHODS

Patients

Three patient cohorts were analyzed. All patients met American Rheumatism Association (ARA) criteria for RA (11) at some time. These studies were approved by the Vanderbilt Institutional Review Board for the protection of human subjects.

The 1985 cohort included 210 patients who were identified at 3 sites, the weekly Vanderbilt University rheumatology clinic of TP, as well as the Nashville Veterans Administration Medical Center, and the private practice of Dr. Joseph Huston in Nashville. This cohort had been assembled in 1984-86 to provide baseline data for a longitudinal observational study to analyze whether a modified health assessment questionnaire (MHAQ) would predict premature mortality prospectively in patients with RA, as a patient questionnaire at baseline in 1973 had been found to be a significant predictor of survival over 9 years in 1984 retrospective analyses (12). The newer cohort to be observed prospectively would also have available quantitative joint count, radiographic scores and laboratory tests, which had not been available at baseline for the earlier cohort. In order to compare patients in the same rheumatology clinical setting 15 years apart, only the 125 consecutive patients seen at by TP Vanderbilt University are included in this report; the 85 patients seen at the 2 other sites are not included, particularly as data from the Veterans Administration Medical Center may have biased the results toward poorer status in 1985.

The mean age of the 125 patients in the 1985 Cohort was 55 (range 30-87) years; 65% of the patients were female, 86% were Caucasian, and 86% were rheumatoid factor positive. The mean formal education level was 11 years, and mean duration of disease 9.6 years. Among all patients, 63% took a disease modifying anti-rheumatic drug (DMARD) including prednisone, 33% took any DMARD not including prednisone (30% took only prednisone) and only 10% took methotrexate. Further data concerning this cohort are found in previous reports (9;13-18).

The 2000 RA cohort included 152 consecutive patients with RA who were seen between January 1998 and June 2001 by the same rheumatologist (TP) at the same weekly academic rheumatology clinic. These patients had been under care of this rheumatologist for a mean of 4.6 years (range 0-19 years) and had a mean duration of 12.5 years of disease. Twelve patients did not have a joint count recorded and another 2 were taking biologic agents; therefore, 138 patients are included in this report. The mean age of the 138 (of 152 patients) in the 2000 Cohort was 58 years; 72% of the patients were female, 94% were Caucasian, and 58% rheumatoid factor positive. The mean formal education level was 13 years, and mean duration of disease 12.6 years. These patients were treated more aggressively according to a philosophy of attempting to control inflammation as completely as possible in order to prevent long-term damage (19); 87% took DMARDs including prednisone and 67% took methotrexate. Further data concerning this cohort are found in previous reports (7-9).

A 2001 RA cohort included 232 patients of 5 rheumatologists at Arthritis Specialists of Nashville seen between February and October 2001, with symptoms which began in 1998 or later. All were under care in Nashville, TN, USA, but none were under care of TP at Vanderbilt University. Potentially eligible patients were identified through review of medical records on the day before scheduled appointments and through the treating physicians who identified new patients. The study was described
by the treating physician to appropriate patients; more than 90% of patients who were
asked agreed to enroll in an early rheumatoid arthritis treatment evaluation registry
(ERATER), and completed written informed consent for current and future monitoring.

The mean age of the 232 patients in the early 2001 “early RA” Cohort was 54
years; 77% were female, 90% were Caucasian, 74% were rheumatoid factor positive.
The mean level of formal education was 13 years and the mean duration of disease at
study visit was 1.8 years or 21 months. The mean duration of symptoms was 5.1
months before the diagnosis. At the study visit, 22 (9.5%) of patients had RA symptoms
for less than 6 months, 45 (19.4%) had symptoms 6-12 months, 64 (27.6%) 1-2 years,
and 101 (43.5%) more than 2 years. These patients were also treated aggressively;
99% took DMARDs including prednisone, and 91% took DMARDs not including
prednisone, including 80% took methotrexate. Further data concerning this cohort are
found in previous reports (7;8;20;21).

Measures of clinical status

All patients were evaluated according to what has become known as a “standard
protocol to evaluate rheumatoid arthritis” (SPERA) (22). This protocol includes all
measures in the ACR Core Data Set to assess clinical status in RA (5), and the disease
activity score (DAS) (1-3). In this report, only the joint count data are analyzed. A 28
joint count includes 10 proximal interphalangeal (PIP) joints of the hands, 10
metacarpophalangeal (MCP) joints, 2 wrists, 2 elbows, 2 shoulders and 2 knees (3;16).
The 42 joint count includes these joints plus 2 hips and 2 ankles, and 10
metatarsophalangeal (MTP) joints (8).
**Statistical Analyses**

All data were entered into a microcomputer using Access software, with data entry and data management programs developed specifically for the SPERA review. The data were transferred to Statistical Package for the Social Sciences (SPSS 11.0 Chicago, IL) for the personal computer and analyzed according to descriptive statistics. The numbers of patients according to 12, 6, 5, 4, 3, 2 and 1 tender or swollen joints were analyzed as cross tabulations. Probability plots were computed to depict the proportion of patients found at continuous levels.

**RESULTS**

**Tender joint counts**

In the 1985 Cohort, on a 28 joint count (Figure 1), 79.9% of patients had 6 or more tender joints, compared to 37% of patients in the 2000 Cohort and 36.6% of the 2001 “early RA” Cohort. On a 42 joint count, 50.4% of the 2001 “early RA” patients had 6 or more tender joints (Figure 1). Three or more tender joints were seen in 89.5% of the 1985 Cohort, 48.6% of the 2000 Cohort, and 57.8% of the 2001 “early RA” Cohort on a 28 joint count, as well as 66.4% of the 2001 “early RA” Cohort on a 42 joint count (Figure 1). More patients in the 1985 cohort had 6 or more tender joints on a 28 joint count (79.9%) than had even >1 tender joint in the 2000 Cohort (66.7%), and a similar proportion (79.8%) had >1 tender joint in the 2001 “early RA” Cohort. Furthermore, almost as many patients had 2 tender joints on a 42 joint count in the 2001 “early RA” Cohort (77.2%) as had 6 or more tender joints on a 28 joint count in the 1985 Cohort (79.9%).
Swollen joint counts

In the 1985 Cohort, on a 28 swollen joint count (Figure 2), 78.2% of patients had 6 or more swollen joints, compared to 50% of patients in the 2000 Cohort, and 46.1% of the 2001 “early RA” Cohort. On a 42 joint count, 63.4% of the 2001 “early RA” patients had 6 or more swollen joints (Figure 2). Three or more swollen joints were seen in 90.3% of the 1985 Cohort, 67.4% of the 2000 Cohort, and 72.0% of the 2001 “early RA” Cohort on a 28 joint count. Furthermore, 84.1% of the 2001 “early RA” Cohort had 3 or more swollen joints on a 42 joint count (Figure 2). More patients in the 1985 Cohort had 6 or more swollen joints on a 28 joint count (78.2%) than had ≥2 swollen joints in the 2000 Cohort (73.2%) or ≥3 swollen joints in the 2001 “early RA” Cohort (72%). Furthermore, about as many patients had ≥4 swollen joints in the 2001 “early RA” Cohort on a 42 joint count (76.8%) as had 6 or more swollen joints on a 28 joint count in 1985 (78.2%).

Percentiles of tender and swollen joints

Each of the 3 cohorts were analyzed as percentiles of tender and swollen joint counts (Table 1). The 50th percentile for tender joints on a 28 joint count was 11 for the 1985 Cohort, 2 for the 2000 Cohort, and 4 for 2001 “early RA” Cohort; on a 42 joint count, the 50th percentile was 6 for the 2001 “early RA” Cohort (Table 1). Seven tender joints were seen in the 30th percentile in the 1985 Cohort, compared to the 70th percentile with 9 swollen joints in the 2000 Cohort and 8 swollen joints in the 2001 “early RA” Cohort, and 50th percentile values of 8 on a 42 joint count in the 2001 “early RA” Cohort (Table 1).

The cumulative proportion of patients at various levels of tender joints and swollen joints are depicted as probability plots (Figure 3). The probability plots again illustrate that 78%-80% of patients had 6 tender or 6 swollen joints in 1985 compared to only 37%-50% in 2000 Cohort and 2001 “early RA” Cohort.

DISCUSSION

In theory, a clinical trial of a new agent in any disease might include all consecutive patients who meet criteria for the diagnosis under study. Pragmatically, that is not possible, in part because some patients may have too little disease activity to be appropriate candidates for evaluation of a new therapy. In population-based studies of people who meet criteria for RA, more than half do not have progressive disease (23-25). Some of these people may have reactive arthritis and other forms of self-limited inflammatory arthritis, rather than progressive RA. Therefore, it is reasonable to include only patients with a given level of severity of disease activity in order to recognize possible responses to therapy.

The DAS (1-3) and Core Data Set (4-6) have provided important advances in rheumatology clinical research, leading to standardized primary outcomes in RA clinical trials over the last decade. However, inclusion criteria in trials have remained similar to those of 2 decades ago, although the status of patients in recent studies appears to have improved substantially compared to previous decades (9;26-31). Differences
between the 1985 versus the 2000 and 2001 “early RA” Cohorts may be explained in part by responses to aggressive therapy, as only 10% of patients were taking methotrexate in 1985 compared to 67-80% in 2000 and 2001 (9). Furthermore, biologic agents were available in 2000 and 2001, although the two patients in 2000 cohort who were taking biologic agents were excluded from then analyses and fewer than 5% of the 2001 patients in this study were taking these agents at the time of the study. However, a secular trend to milder disease may also be present (9;32).

The percentiles presented in this report provide an approach to “benchmarking” of clinical status in cohorts of RA patients, applied by Lassere et al (33), Wiles et al (34), Wolfe and Choi (35), and Krishnan et al (36). In this study, the focus is the change in joint count data. The 42 joint count data are presented to document that results are similar to the 28 joint count, in large part as the 28 joint count includes the joints most likely to be abnormal in patients with RA (16). The 2001 cohort was included in part so that patients of rheumatologists other than TP could be analyzed.

Several limitations are seen in these studies. First, the data presented are derived from only 2 clinical settings in one city, Nashville, TN, USA. However, data from an earlier Nashville Cohort concerning functional declines (12), work disability (12), socio-economic status and RA status (37), and premature mortality (12;38) proved generalizable to other sites (39;40). Furthermore, data from the 1985 Cohort, which was recruited in the same setting as the 2000 Cohort, also have proved generalizable to other sites (39;40), including reports concerning radiographic damage (15), a 28 joint count (16), the absence of correlation between joint tenderness and pain compared to radiographic findings (14), laboratory associations of HLA-DR4 with radiographic changes but not with measures of function (13), reliability of physical measures of functional status (18), correlations of patient questionnaire scores for functional status with traditional measures (17), work disability (41), socio-economic status and RA status (42-44) and premature mortality (44). A second limitation is that other inclusion and exclusion criteria beyond the joint count may affect generalizability of clinical trials, such as exclusions for age, comorbidities, ESR or CRP, as well as safety considerations and administrative issues. As noted, the focus in this study is the change in joint count data.

The 3 cohorts studied provide an unusual opportunity to analyze in depth patients with RA in two different eras, 1985 versus 2000 and 2001, as most standard rheumatology care is conducted without quantitative data outside of laboratory tests. It appears that common joint count inclusion criteria for RA clinical trials were met by a majority of patients in 1985 and were not met in 2000 and 2001. The results may suggest consideration of revision of common joint count inclusion criteria for contemporary RA clinical trials.

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Table 1. Percentiles of tender joint and swollen joint counts in 3 cohorts of patients with rheumatoid arthritis: 28 joint count in a 1985 Cohort – 125 patients seen in 1984-1986; 28 joint count in a 2000 Cohort - 138 patients seen in 1998-2001; 28 and 42 joint counts in a 2001 “early RA” Cohort – 232 patients whose mean disease duration was 1.8 years.

<table>
<thead>
<tr>
<th>Percentile</th>
<th>Tender Joint Count</th>
<th>Swollen Joint Count</th>
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<tbody>
<tr>
<td></td>
<td>Cohort:</td>
<td></td>
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<tr>
<td>10</td>
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Figure 1. Percentages of patients with different numbers of tender joints in 3 cohorts of patients with rheumatoid arthritis: 28 joint count in a 1985 Cohort – 125 patients seen in 1984-1986; 28 joint count in a 2000 Cohort - 138 patients seen in 1998-2001; 28 and 42 joint counts in a 2001 “early RA” Cohort – 232 patients seen in 2001 whose mean disease duration was 1.8 years.

Figure 2. Percentages of patients with different numbers of swollen joints in 3 cohorts of patients with rheumatoid arthritis: 28 joint count in a 1985 Cohort – 125 patients seen in 1984-1986; 28 joint count in a 2000 Cohort - 138 patients seen in 1998-2001; 28 and 42 joint counts in a 2001 “early RA” Cohort – 232 patients whose mean disease duration was 1.8 years.

Figure 3. Probability plots illustrating the cumulative percent of patients in 3 cohorts of patients with rheumatoid arthritis, according to the number of swollen joints and number of tender joints on a 28 joint count in 1985, 2000 and 2001, and a 42 joint count in 2001.
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Figure 1

1985 Cohort: Tender Joints (0-28)

- >=12 joints: 46.8%
- >=6 joints: 79.9%
- >=4 joints: 84.7%
- >=3 joints: 89.5%
- >=2 joints: 94.3%
- >=1 joint: 96.7%
- >=0 joints: 100.0%

2001 Cohort E: Tender joints (0-28)

- >=12 joints: 17.2%
- >=6 joints: 36.6%
- >=4 joints: 50.0%
- >=3 joints: 57.8%
- >=2 joints: 69.0%
- >=1 joint: 79.8%
- >=0 joints: 100.0%

2000 Cohort L: Tender joints (0-28)

- >=12 joints: 19.6%
- >=6 joints: 37.0%
- >=4 joints: 43.5%
- >=3 joints: 48.6%
- >=2 joints: 58.7%
- >=1 joint: 66.7%
- >=0 joints: 100.0%

2001 Cohort E: Tender joints (0-42)

- >=12 joints: 29.7%
- >=6 joints: 50.4%
- >=4 joints: 61.2%
- >=3 joints: 66.4%
- >=2 joints: 77.2%
- >=1 joint: 86.3%
- >=0 joints: 100.0%
Figure 2.

1985 Cohort: Swollen Joints (0-28)
- >=12 joints: 50.8%
- >=6 joints: 78.2%
- >=4 joints: 86.3%
- >=3 joints: 90.3%
- >=2 joints: 95.1%
- >=1 joint: 97.5%
- >=0 joints: 100.0%

2001 Cohort E: Swollen joints (0-28)
- >=12 joints: 14.2%
- >=6 joints: 46.1%
- >=4 joints: 58.2%
- >=3 joints: 72.0%
- >=2 joints: 81.1%
- >=1 joint: 89.3%
- >=0 joints: 100.0%

2000 Cohort L: Swollen joints (0-28)
- >=12 joints: 20.3%
- >=6 joints: 50.0%
- >=4 joints: 63.8%
- >=3 joints: 67.4%
- >=2 joints: 73.2%
- >=1 joint: 79.0%
- >=0 joints: 100.0%

2001 Cohort E: Swollen joints (0-42)
- >=12 joints: 29.3%
- >=6 joints: 63.4%
- >=4 joints: 76.8%
- >=3 joints: 84.1%
- >=2 joints: 88.7%
- >=1 joint: 93.6%
- >=0 joints: 100.0%
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