EXTENDED REPORT

Declines in number of tender and swollen joints in patients with rheumatoid arthritis seen in standard care in 1985 versus 2001: possible considerations for revision of inclusion criteria for clinical trials

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Ann Rheum Dis 2006;65:878–883. doi: 10.1136/ard.2005.044131

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Accepted
9 November 2005
Published Online First
8 December 2005

Objective: To analyse tender and swollen joint counts in three cohorts of patients with rheumatoid arthritis (RA), with a focus on the proportions of patients who had fewer than 6–12 tender or swollen joints, as possible evidence based information toward more generalisable inclusion criteria for current and future RA clinical trials.

Methods: Tender and swollen joint counts were analysed in three cohorts of patients with RA: 125 in 1985, 138 in 2000, and 232 with early RA in 2001.

Results: The median numbers of tender joints were 11, 2, and 4 in 1985, 2000, and in early RA in 2001, respectively. The median numbers of swollen joints were 12, 6, and 5 in 1985, 2000, and 2001, respectively. The numbers of tender joints among 28 assessed were ≥ 12 , ≥ 6 , ≥ 4 , and ≥ 3 in 47%, 80%, 85%, and 90% of patients in 1985; 20%, 37%, 44%, and 49% in 2000; and 17%, 37%, 50%, and 58% in early RA in 2001. The numbers of swollen joints among 28 assessed were ≥ 12 , ≥ 6 , ≥ 4 , and ≥ 3 in 51%, 78%, 86%, and 90% of patients in 1985; 20%, 50%, 64%, and 67% in 2000; and 14%, 46%, 58%, and 72% in 2001. The number of patients with ≥ 6 tender or swollen joints in 1985 was greater than the number with ≥ 3 joints in 2000 and in early RA in 2001.

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

The joint count is the most specific clinical measure to assess disease activity in patients with rheumatoid arthritis (RA). A tender and swollen joint count is included in the Disease Activity Score (DAS)^{1–3} and American College of Rheumatology 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 six or more swollen or tender joints.^{7,8} Furthermore, the 2000 cohort appeared to have substantially more favourable clinical status than a cohort of patients seen in the same setting in 1985, most of whom did have six or more tender and swollen joints in 1985.⁹

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. A reduced number of tender and/or swollen joints required for inclusion might improve generalisability of contemporary and future RA clinical trials. However, relatively little published data are available about the specific number of tender or swollen joints, (particularly fewer than six), found in patients outside clinical trials, as formal joint counts are usually not performed by most rheumatologists in standard care.¹⁰ Therefore, in this report, we analyse the prevalence of 0– ≥ 12 tender or swollen joints in patients in the three cohorts from standard care.

PATIENTS AND METHODS

Patients

Three patient cohorts were analysed. All patients had met American Rheumatism Association criteria for RA¹¹ 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 three sites, the weekly Vanderbilt University rheumatology clinic of TP, 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 analyse whether a modified Health Assessment Questionnaire would predict premature mortality prospectively in patients with RA after a retrospective analysis in 1984 indicated that a patient questionnaire was a significant predictor of survival over 9 years.¹² The newer cohort to be observed prospectively would also have available a quantitative joint count, radiographic scores, and laboratory tests, which had not been available at baseline for the earlier cohort. To compare patients in the same rheumatology clinical setting 15 years apart, only the 125 consecutive patients seen by TP at Vanderbilt University are included in this report; the 85 patients seen at the two other sites are not included, particularly as data from the Veterans Administration Medical Center might have biased the results toward poorer status in 1985.

The mean age of the 125 patients in the 1985 cohort was 55 years (range 30–87); 65% of the patients were female, 86% were white, 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

Abbreviations: DAS, Disease Activity Score; DMARD, disease modifying antirheumatic drug; RA, rheumatoid arthritis; SPERA, standard protocol to evaluate rheumatoid arthritis

a disease modifying antirheumatic drug (DMARD) including prednisone, 33% took any DMARD not including prednisone (30% took only prednisone), and only 10% took methotrexate. Further data about this cohort can be 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 the care of this rheumatologist for a mean of 4.6 years (range 0–19) and had a mean duration of 12.5 years of disease. Twelve patients did not have a joint count recorded and another two were taking biological 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 white, 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 damage¹⁹; 87% took DMARDs including prednisone and 67% took methotrexate. Further data about this cohort can be found in previous reports.^{7–9}

A 2001 RA cohort included 232 patients of five rheumatologists at Arthritis Specialists of Nashville seen between February and October 2001, with symptoms which began in 1998 or later. All were receiving care in Nashville, TN, USA, but none were under the care of TP at Vanderbilt University. Potentially eligible patients were identified through a review of medical records on the day before scheduled appointments and through the treating physicians who identified new patients with RA. The study was described by the treating physician to appropriate patients; more than 90% of patients who were asked agreed to enrol in an early rheumatoid arthritis treatment evaluation registry (ERATER), and gave 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 white, 74% were rheumatoid factor positive. The mean level of formal education was 13 years and the mean duration of disease at the 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 had RA symptoms for less than 6 months, 45 (19.4%) for 6–12 months, 64 (27.6%) for 1–2 years, and 101 (43.5%) for more than 2 years. These patients were also treated aggressively; 99% took DMARDs including prednisone, and 91% took DMARDs not including prednisone, including 80% who took methotrexate. Further data about this cohort can be 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 American College of Rheumatology 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 analysed. A 28 joint count includes 10 proximal interphalangeal joints of the hands, 10 metacarpophalangeal 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 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 analysed according to descriptive statistics. The numbers of patients according to 12, 6, 5, 4, 3, 2, and 1 tender or swollen joints were analysed 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 (fig 1), 79.9% of patients had six or more tender joints, compared with 37.0% 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 patients with “early RA” had six or more tender joints (fig 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 (fig 1). More patients in the 1985 cohort had six 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 two tender joints on a 42 joint count in the 2001 “early RA” cohort (77.2%) as had six 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 (fig 2), 78.2% of patients had six or more swollen joints, compared with 50.0% 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 patients with “early RA” had six or more swollen joints (fig 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 three or more swollen joints on a 42 joint count (fig 2). More patients in the 1985 cohort had six 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 (72.0%). Furthermore, about as many patients had ≥ 4 swollen joints in the 2001 “early RA” cohort on a 42 joint count (76.8%) as had six or more swollen joints on a 28 joint count in 1985 (78.2%).

Centiles of tender and swollen joints

Each of the three cohorts was analysed as centiles of tender and swollen joint counts (table 1). The 50th centile for tender joints on a 28 joint count was 11 for the 1985 cohort, 2 for the 2000 cohort, and 4 for the 2001 “early RA” cohort; on a 42 joint count, the 50th centile was 6 for the 2001 “early RA” cohort (table 1). Seven tender joints were seen in the 30th centile in the 1985 cohort, compared with the 70th centile in both the 2000 and 2001 “early RA” cohorts on a 28 joint count.

Similarly, the 50th centile for swollen joints was 12 in the 1985 cohort, 6 in the 2000 cohort, and 5 in the 2001 “early RA” cohort, and 8 in the 2001 “early RA” cohort on a 42 joint count (table 1). The 30th centile value of 8 swollen joints in the 1985 cohort was similar to the 70th centile with 9 swollen joints in the 2000 cohort and 8 swollen joints in the 2001 “early RA” cohort, and 50th centile values of 8 on a 42 joint count in the 2001 “early RA” cohort (table 1).

Figure 3 depicts the cumulative proportion of patients at various levels of tender joints and swollen joints as probability plots. The probability plots again illustrate that 78–80% of patients had six tender or six swollen joints in

Figure 1 Percentages of patients with different numbers of tender joints in three cohorts of patients with RA: 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 three cohorts of patients with RA: 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 1 Centiles of tender joint and swollen joint counts in three cohorts of patients with rheumatoid arthritis*

Centile	Tender joint count in cohort:				Swollen joint count in cohort			
	1985 (28 joint count)	2000 (28 joint count)	2001 (28 joint count)	2001 (42 joint count)	1985 (28 joint count)	2000 (28 joint count)	2001 (28 joint count)	2001 (42 joint count)
10	2	0	0	0	3	0	0	1
20	5	0	0	1	5	0	2	3
30	7	0	1	2	8	2	3	5
40	9	1	2	4	10	4	3	6
50	11	2	4	6	12	6	5	8
60	13	4	5	8	13	7	6	9
70	16	7	7	11	15	9	8	11
80	19	11	10	15	18	12	9	13
90	23	18	15	22	22	15	13	20

*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.

1985 compared with 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 treatment. 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 recognise possible responses to treatment.

The DAS^{1–3} and Core Data Set^{4–6} have provided important advances in rheumatology clinical research, leading to standardised primary outcomes in RA clinical trials over the past decade. However, inclusion criteria in trials have remained similar to those of two decades ago, although the status of patients in recent studies appears to have improved substantially compared with 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 treatment, as only 10% of patients were taking methotrexate in 1985 compared with 67–80% in 2000 and

2001.⁹ Furthermore, biological agents were available in 2000 and 2001, although the two patients in 2000 cohort who were taking biological agents were excluded from the 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 centiles presented in this report provide an approach to “benchmarking” the clinical status in cohorts of patients with RA, 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 show that results are similar to those of 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 analysed.

These studies have several limitations. Firstly, the data presented are derived from only two clinical settings in one city, Nashville, TN, USA. However, data from an earlier Nashville cohort concerning functional declines,¹² work disability,¹² socioeconomic status and RA status,³⁷ and premature mortality^{12 38} proved generalisable 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 generalisable to other sites,^{39 40} including reports about radiographic damage,¹⁵ a 28 joint count,¹⁶ the absence of correlation between joint tenderness and pain compared

Figure 3 Probability plots illustrating the cumulative percentage of patients in three cohorts of patients with RA, according to the number of swollen joints and number of tender joints on a 28 joint count in 1985, 2000, and 2001.

with 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 socioeconomic 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 generalisability of clinical trials, such as exclusions for age, comorbidities, erythrocyte sedimentation rate or C reactive protein, as well as safety considerations and administrative issues. As noted, the focus in this study is the change in joint count data.

The three cohorts studied provide an unusual opportunity to analyse in depth patients with RA in two different eras, 1985 versus 2000 and 2001, as most standard rheumatology care is conducted with no quantitative data outside those 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 suggest that revision of common joint count inclusion criteria should possibly be considered for contemporary RA clinical trials.

ACKNOWLEDGEMENTS

We thank Drs Joseph H Huston III, David S Knapp, M Porter Meadors, Kevin J Myers, and Paul W Wheeler for generous cooperation and encouragement of their patients to participate in the 2001 "early RA" cohort, Melissa Gibson and Christopher Swearingen for helpful technical assistance. Supported in part by grants from Pfizer, Pharmacia, the Jack C Massey Foundation, and by NIH grant HL 67964.

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