Most Patients Receiving Routine Care for Rheumatoid Arthritis in 2001 Did Not Meet Inclusion Criteria for Most Recent Clinical Trials or American College of Rheumatology Criteria for Remission

TUULIKKI SOKKA and THEODORE PINCUS

ABSTRACT. ***Objective.*** To determine the proportion of 2 cohorts of patients with rheumatoid arthritis (RA) in Nashville, Tennessee, who met 4 common criteria for inclusion in clinical trials: ≥ 6 swollen joints, ≥ 6 tender joints, erythrocyte sedimentation rate ≥ 28 mm/h, and/or morning stiffness ≥ 45 min.

Methods. Two cohorts of patients with RA, all of whom had met American Rheumatism Association (ARA) [now American College of Rheumatology (ACR)] criteria for RA at some time, were studied. Cohort L (late) included 146 consecutive patients whose mean disease duration was 14.0 years and who had been under care at a weekly academic rheumatology clinic for a mean of 6.2 years when seen in 1998–2001. Cohort E (early) included 232 patients of 5 private practice rheumatologists whose symptoms began in 1998 or later and whose mean disease duration was 1.8 years when seen in 2001. Patients were reviewed for the 4 inclusion criteria as well as 6 ARA remission criteria.

Results. In Cohort L, on a 28 joint count, 42.5% of patients had ≥ 6 swollen joints, 25.3% had ≥ 6 tender joints, 19.9% had both ≥ 6 swollen and ≥ 6 tender joints, 25.0% had ESR ≥ 28, and 45.9% had morning stiffness ≥ 45 min. In Cohort E, on a 42 joint count, 63.4% of patients had ≥ 6 swollen joints, 50.4% had ≥ 6 tender joints, 38.8% had both ≥ 6 swollen and ≥ 6 tender joints, 49.3% had ESR ≥ 28, and 50.9% had morning stiffness ≥ 45 min. Overall, 15.3% of Cohort L and 34.1% of Cohort E patients had ≥ 6 swollen and tender joints, as well as an ESR ≥ 28 or morning stiffness ≥ 45 min. Only 4.1% of Cohort L and no patient in Cohort E met ARA criteria for remission.

Conclusion. The majority of patients seen in routine care in these 2 cohorts did not meet criteria for inclusion in most contemporary RA clinical trials, including clinical trials sponsored by pharmaceutical companies to introduce new drugs or biological agents. Few of these patients met ARA criteria for remission. Controlled trial data are not available concerning results of treatment with new biological agents or disease modifying antirheumatic drugs in a large proportion, if not a majority, of patients with RA at this time. (J Rheumatol 2003;30:1138–46)

Key Indexing Terms:
RHEUMATOID ARTHRITIS INCLUSION CRITERIA CLINICAL TRIAL

Randomized controlled clinical trial data that document the efficacy of a drug versus a placebo are required for approval of a new therapy to be marketed to patients[1]. The clinical trial is designed to study as uniform a group of patients as possible, to focus on the test variable — the drug versus placebo or another drug. This goal requires inclusion and exclusion criteria for patients who enter the trial. Most clinical trials conducted in patients with rheumatoid arthritis (RA) over the last decade[2-25] have listed relatively similar inclusion criteria, such as 6 or more swollen joints, 6 or more tender joints, an erythrocyte sedimentation rate (ESR) of 28 or more, and/or morning stiffness of 45 minutes or more (Table 1).

Little information is available concerning the proportion of patients seen in routine rheumatology care settings who meet common criteria for inclusion in clinical trials. We observed that many patients with RA receiving standard care in our clinic did not meet inclusion criteria for many clinical trials, including the Anti-Tumor Necrosis Factor Trial in RA with Concomitant Therapy (ATTRACT) trial of infliximab plus methotrexate versus methotrexate[18-20] and the Early Rheumatoid Arthritis (ERA) trial of etanercept versus methotrexate[24,25], and extended this observation to analyze important limitations of the randomized clinical trial methodology in rheumatic diseases[26-29]. In this report, we present further analyses of patients who received routine clinical care in 2 settings in Nashville, Tennessee, USA,

From the Division of Rheumatology and Immunology, Vanderbilt University School of Medicine, Nashville, Tennessee, USA.

Supported in part by grants from Aventis, Amgen, Pharmacia, the Jack C. Massey Foundation, the Academy of Finland, and by National Institutes of Health Grant HL 67964.

T. Sokka, MD, PhD, Vanderbilt University and Jyväskylä Central Hospital, Jyväskylä, Finland; T. Pincus, MD, Vanderbilt University.

Address reprint requests to Dr. T. Sokka, Division of Rheumatology and Immunology, Vanderbilt University School of Medicine, 203 Oxford House, Box 5, Nashville, TN 37232-4500. E-mail: tuulikki.sokka@vanderbilt.edu

Submitted June 11, 2002; revision accepted December 6, 2002.

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Table 1A. Inclusion criteria in selected clinical trials in RA. Nonbiological agents.

Trial	Mean Disease Duration, yrs	Inclusion Criteria for Disease Activity (and Required Treatments Prior to the Study)	Mean Swollen Joint Count	Mean Tender Joint Count	No. Joints Analyzed	Therapy
Tugwell 1990[2]	10.9, 11.1	≥ 6 swollen or tender joints + 2 of 3: ≥ 9 tender joints; ESR ≥ 28; AM ≥ 45 (+ failed gold or D-pen)	14.6, 14.3			CyA vs Pbo
Ahern 1991[3]	8.9, 9.2	≥ 3 swollen joints + 2 of 3: ≥ 6 tender joints; ESR > 30; AM ≥ 45 (+ failed gold or D-pen)	6, 5	17, 16		CyA vs AZA
Tugwell 1995[4]	9, 4, 11.2	≥ 6 swollen or tender joints	15, 2, 17.3	18.9, 20.4	66 swollen, 68 tender	CyA + MTX vs Mtx + Pbo
Zeidler 1998 [5]	0.9, 1.0	3 of 4: ≥ 3 swollen joints; ≥ 6 tender joints; ESR ≥ 28 or CRP ≥ 20; AM ≥ 60 min + erosions or failed a DMARD + 2 of 3: RF+; ESR ≥ 40 or CRP > 40; Hgb < 110	8.6, 8.7			CyA vs IM gold
Yocum 2000[6]	11.1, 10.8	3 of 4: ≥ 3 swollen joints; ≥ 6 tender joints; ESR ≥ 28 or CRP ≥ 20; AM ≥ 60			66 swollen, 68 tender	CyA 2 formulas
Weinblatt 1999[7]	13.6	≥ 8 swollen and ≥ 10 tender joints + 1 of 2: ESR ≥ 28; AM ≥ 45	16.3	16.9	28	Leflunomide + MTX
Smolen 1999[8]	7.6, 5.7, 7.4	≥ 6 swollen and ≥ 6 tender joints + ESR > 28 or CRP > 20 + physician and patient global 'fair,' poor,' or 'very poor'	16.2, 15.8, 15.3	18.8, 16.3, 16.7	28	Leflunomide vs Pbo vs SSZ
Strand 1999[9,10]	7.0, 6.9, 6.5	3 of 4: ≥ 6 swollen joints; ≥ 9 tender joints; ESR ≥ 28; AM ≥ 45	13.7, 14.8, 13.0	15.5, 16.5, 15.8	28	Leflunomide vs Pbo vs MTX
Trentham 1993[11]	9.8, 10.3	3 of 4: ≥ 6 swollen joints; ≥ 9 tender joints; ESR ≥ 28; AM ≥ 45 (+ failed one immuno-suppressive drug)	11.8, 12.0	15.8, 15.6		Collagen vs Pbo
Furst 2000[12]	14.6, 17.4	≥ 10 swollen joints and ≥ 20 tender joints and AM ≥ 60 and patient and physician global VAS ≥ 5 (+ failed MTX or 2 other DMARD)	23.9, 23.8	36.7, 36.2		Immunoadsorption vs Pbo
O'Dell 1996[13]	10, 6, 10	3 of 4: ≥ 3 swollen joints; ≥ 8 tender joints; ESR ≥ 28; AM ≥ 45 (+ poor response to gold, HCQ, D-Pen, SSZ, or MTX)	31, 31, 27	31, 32, 29		MTX vs SSZ + HCQ vs MTX + SSZ + HCQ
Boers 1997[14]	all < 2; median duration 4 mo	≥ 6 swollen joints at ≥ 3 sites + 2 of 3: ≥ 9 tender joints; ESR ≥ 28; AM ≥ 45	16, 15	25, 24	48	MTX + SSZ + PRED vs SSZ
Möttönen 1999[15]	all < 2; 0.6, 0.7	≥ 3 swollen joints + 3 of 4: ≥ 5 swollen and ≥ 10 tender joints; ESR ≥ 28; CRP ≥ 19; AM ≥ 29	13, 14	18, 20	66 swollen, 68 tender	MTX + SSZ + HCQ + PRED vs SSZ

D-pen: D-penicillamine; ESR: erythrocyte sedimentation rate, mm/h; CRP: C-reactive protein, mg/l; AM: morning stiffness, min; CyA: cyclosporin A; Pbo: placebo; MTX: methotrexate; IM gold: intramuscular gold; SSZ: sulfasalazine; HCQ: hydroxychloroquine; PRED: prednisone.

between 1998 and 2001 to determine the proportion of patients who met the 4 common criteria noted above for inclusion in clinical trials. As clinical remission is one possible basis for patients not meeting inclusion criteria, we also identified patients who met American Rheumatism Association (ARA) [now American College of Rheumatology (ACR)] criteria for remission[30].

MATERIALS AND METHODS

Patients. Two patient cohorts were analyzed. All patients met ARA criteria for RA[31] at some time. These studies were approved by the Vanderbilt University Institutional Review Board for the protection of human subjects.

Cohort L (late) included all 152 patients with RA who were seen between January 1998 through June 2001 by the senior rheumatologist (TP) at a weekly academic rheumatology clinic. These patients had been under care of this rheumatologist for a mean of 6.2 years (range 0–19 yrs). Six patients did not have a joint count recorded, therefore 146 patients are included in this report. Patients are treated aggressively according to a philosophy of attempting to control inflammation as completely as possible in order to prevent longterm damage[32-39].

Cohort E (early) included 232 patients with recent-onset RA seen by 5 full-time rheumatologists at Medical Specialists of Nashville (now Arthritis Specialists of Nashville), whose symptoms began in 1998 or later and were seen between February and October 2001. Potentially eligible patients for Cohort E were identified through review of medical records on the day before scheduled appointments, and through the treating physicians to identify new patients. The study was described by the treating physician to appropriate patients. More than 90% of patients who were asked agreed to participate and completed written informed consent for current and future monitoring.

Many patients were seen multiple times over this period. In this report, the last visit that included a detailed joint count is regarded as the study visit. In another report concerning these cohorts[29], we analyzed the first (rather than the last) visit to attempt to maximize eligibility for 2 specific clinical trials, the ATTRACT trial of infliximab plus methotrexate (MTX) versus MTX[18-20] in Cohort L, and the early RA (ERA) trial of etanercept versus MTX[24,25] in Cohort E. In this report, it appeared of greater interest to characterize the disease modifying antirheumatic drugs (DMARD) and

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Table 1B. Inclusion criteria in selected clinical trials in RA. Biological agents.

Trial	Mean Disease Duration, yrs	Inclusion Criteria for Disease Activity (and Required Treatments Prior to the Study)	Mean Swollen Joint Count	Mean Tender Joint Count	No. Joints Analyzed	Therapy
Woodworth 1993[16]		≥ 3 swollen joints and ≥ 6 tender joints and AM ≥ 45 (+ taking MTX)				IL-2 fusion toxin
Snowden 1998[17]	9, 12, 6	≥ 6 swollen joints and ≥ 6 tender joints + 2 of 3: ≥ 9 tender joints; ESR > 28; AM ≥ 60 (+ failed ≥ 2 DMARD)	14, 14, 14	14, 24, 20	28	Filgrastim 5µg vs 10 µg vs Pbo
Maini 1998[18]	7.6–14.3	≥ 6 swollen joints + 2 of 3: ≥ 6 tender joints; ESR > 28; CRP > 15; AM > 45	16–20	17–33	66 swollen, 68 tender	Infliximab multiple doses + MTX; MTX + Pbo
Lipsky 2000[19]	7.2–9.0	≥ 6 swollen and ≥ 6 tender joints + 2 of 3: ESR > 28; CRP > 20; AM ≥ 45 (+ taking MTX ≥ 12.5 mg/week)	19–23	24–35	66 swollen, 68 tender	Infliximab multiple doses + MTX; MTX + Pbo
Bresnihan 1998[21]	3.7–4.3	≥ 10 swollen joints + 3 of 4: ≥ 10 tender joints; "severe" or "very severe" disease activity by patient; "severe" or "very severe" disease activity by physician; CRP > 15	26–27	33–36	66 swollen 68 tender	Anakinra multiple doses vs Pbo
Cohen 2002[22]	6.3–8.0	≥ 6 swollen joints + 2 of 3: ≥ 9 tender joints; CRP > 15; AM ≥ 45 (+ taking MTX ≥ 15.0 mg/week)	17–19	22–28	66 swollen, 68 tender	Anakinra multiple doses + MTX; MTX + Pbo
Weinblatt 1999[23]	13, 13	≥ 6 swollen and ≥ 6 tender joints (+ taking MTX ≥ 10 mg/week)	20, 17	28, 28	68 swollen 71 tender	Etanercept + MTX vs MTX + Pbo
Bathon 2000[24]	All < 3; 1.0, 0.9, 1.0	Positive RF or ≥ 3 bone erosions + ≥ 10 swollen and ≥ 12 tender joints + 1 of 2: ESR ≥ 28; CRP ≥ 20; AM ≥ 45	24, 24, 24	30, 31, 31		Etanercept 15 mg vs 10 mg vs MTX

D-pen: D-penicillamine; ESR: erythrocyte sedimentation rate, mm/h; CRP: C-reactive protein, mg/l; AM: morning stiffness, min; CyA: cyclosporin A; Pbo: placebo; MTX: methotexate; IM gold: intramuscular gold; SSZ: sulfasalazine; HCQ: hydroxychloroquine; PRED: prednisone.

biological agents taken by patients who might meet or not meet general inclusion criteria, as etanercept and infliximab were introduced over the study period. Therefore, we chose to analyze the last visit, leading to minor differences in results presented in our other report. Interested readers are invited to contact the authors for comparisons of results in the first and last visits.

Measures of clinical status. All patients were evaluated according to a standard protocol to evaluate rheumatoid arthritis (SPERA)[40], by TP in Cohort L and TS in Cohort E. Patients completed a Multi-Dimensional Health Assessment Questionnaire (MDHAQ)[41], including a modified HAQ (MHAQ) of 8 activities to assess functional capacity[42,43] and 10 cm visual analog scales (VAS) to assess pain, fatigue and global status, morning stiffness by self-report, and review of systems.

A joint count of 28 joints was performed in Cohort L[44], and included 10 hand proximal (proximal interphalangeal, PIP), 10 metacarpal (metacarpophalangeal, MCP), 2 wrist, 2 elbow, 2 shoulder, and 2 knee joints, each assessed for tenderness or pain on motion, and swelling (except that shoulder joints are not assessed for swelling). The joint count in Cohort E included 42 joints, 2 hip, 2 ankle, and 10 metatarsophalangeal (MTP) joints, in addition to joints on the 28 joint count (hip joints are not assessed for swelling). Each patient also had a radiograph of the hands and feet, which is not included in this report. Laboratory assessments included ESR and rheumatoid factor (RF). Demographic measures and medications were also recorded in the SPERA assessment[40].

Patients were analyzed according to whether they met 4 criteria for inclusion in current RA clinical trials: ≥ 6 swollen joints, ≥ 6 tender joints, ESR ≥ 28, and morning stiffness ≥ 45 min. Patients were also analyzed according to whether they met ACR preliminary criteria for remission[27]: (1) no joint swelling or soft tissue swelling of tendon sheaths; (2) no joint tenderness or pain on motion; (3) normal ESR of < 30 in women and < 20 in men; (4) morning stiffness ≤ 15 min; (5) absence of joint pain by history, interpreted as a pain VAS score of 1 or less on a scale of 0–10; and (6) absence of fatigue, also interpreted as a VAS score of 1 or less on a scale of 0–10. Patients were also analyzed according to the DMARD and biological therapies they were taking or had taken in the past.

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, SPSS Inc., Chicago, IL, USA) for the personal computer and analyzed according to descriptive statistics.

RESULTS

Patients. The mean age of 146 Cohort L patients was 59.4 years (range 30–87), 69.9% of the patients were female, 93.2% were Caucasian, and 59.7% were RF positive (Table 2). The mean formal education level was 13.0 years and mean duration of disease 14.0 years. These patients had been under care in this clinic for a mean of 6.2 years (range 0–19).

The mean age of 232 Cohort E patients was 53.9 years (range 16–88), 77.2% were female, 89.7% were Caucasian, 73.5% were RF positive (Table 2). The mean level of formal education was 12.8 years and the mean duration of disease at study visit was 1.8 years or 20.9 months. The mean duration of symptoms was 5.1 months before the diagnosis. At the study visit, 22 (9.5%) patients had 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%) > 2 years.

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Table 2. Demographic measures and disease outcome measures in 2 cohorts of 146 and 232 patients with RA seen in routine clinical care.

Measure	Mean (median) or % of Total	
	Cohort L	Cohort E
No. of patients	146	232
Demographic measures		
Age, yrs	59.4 (59.4)	53.9 (53.7)
Sex, female, %	69.9	77.2
Race, Caucasian, %	93.2	89.7
Education, yrs	13.0 (12.0)	12.8 (12.0)
Other disease measures		
Duration of disease, yrs	14.0 (11.1)	1.8 (1.7)
RF positive, %	59.7	73.5
Disease outcome measures		
Swollen joint count (0–28)	5.2 (4.0)	5.9 (5.0)
Swollen joint count (0–42)		8.8 (7.5)
Tender joint count (0–28)	4.2 (2.0)	5.7 (3.5)
Tender joint count (0–42)		8.5 (6.0)
ESR	20.7 (15.5)	30.4 (27.0)
Morning stiffness, min	56.9 (30.0)	70.8 (45.0)
Pain score (0–10)	4.0 (3.5)	4.2 (4.1)
Fatigue score (0–10)	4.2 (3.8)	5.1 (5.0)

Table 3. Percentage of patients who met each inclusion criterion for clinical trials, and remission criteria, in 2 cohorts of 146 and 232 patients with RA seen in routine clinical care.

Measure	Cohort L	Cohort E
No. of patients	146	232
Swollen joint count ≥ 6 (0–28), %	42.5	46.1
Swollen joint count ≥ 6 (0–42)		63.4
Tender joint count ≥ 6 (0–28), %	25.3	36.6
Tender joint count ≥ 6 (0–42)		50.4
ESR ≥ 28, %	25.0	49.3
Morning stiffness ≥ 45 min, %	45.9	50.9

Clinical measures. In Cohort L, on a 28 joint count, the mean number of swollen joints was 5.2 and mean number of tender joints was 4.2. The mean ESR was 20.7, and the mean morning stiffness was 56.9 min. The mean pain VAS was 4.0 and mean fatigue VAS score was 4.2 (Table 2).

In Cohort E, on a 42 joint count, the mean number of swollen joints was 8.8 and mean number of tender joints was 8.5. On a 28 joint count, the mean number of swollen joints was 5.9 and the mean number of tender joints 5.7. The mean ESR was 30.4 and the mean morning stiffness was 70.8 min. The mean pain VAS was 4.2 and the mean fatigue VAS score was 5.1 (Table 2).

Analyses according to inclusion criteria for RA clinical trials. In Cohort L (Table 3), on a 28 joint count, 62 patients (42.5%) had ≥ 6 swollen joints, 37 patients (25.3%) had ≥ 6 tender joints, and 29 patients (19.9%) had both ≥ 6 swollen and ≥ 6 tender joints.

An ESR ≥ 28 was seen in 36 of 144 patients (2 missing values) (25.0%) (Table 3). Among these 36 patients, 21 (14.6% of 144 patients) had ≥ 6 swollen joints, and 10 (6.9% of 144 patients) had ≥ 6 swollen and tender joints (Table 4).

Morning stiffness ≥ 45 min was reported by 67 patients (45.9%) (Table 3). Among these 67 patients, 33 (22.6% of all patients) had ≥ 6 swollen joints, and 20 (13.7% of all patients) had ≥ 6 swollen and ≥ 6 tender joints (Table 4).

Twenty-two patients (15.3% of all patients) had ≥ 6 swollen joints and ≥ 6 tender joints, as well as either morning stiffness ≥ 45 min or an ESR ≥ 28 (Table 4). Only 8 patients (5.6%) had ≥ 6 swollen joints and ≥ 6 tender joints, as well as both morning stiffness ≥ 45 min and an ESR ≥ 28.

In Cohort E (Table 3), on a 28 joint count, 107 patients (46.1%) had ≥ 6 swollen joints, 85 patients (36.6%) had ≥ 6 tender joints. On a 42 joint count, 147 patients (63.4%) had ≥ 6 swollen joints, 117 patients (50.4%) had ≥ 6 tender joints, and 90 patients (38.8%) had both ≥ 6 swollen and ≥ 6 tender joints (Table 5).

An ESR ≥ 28 was seen in 112 of 227 patients (5 missing values) (49.3%). Among these 112 patients, 56 (24.7% of 227 patients) also had ≥ 6 swollen joints and ≥ 6 tender joints (Table 5).

Morning stiffness ≥ 45 min was reported by 113 patients (50.9% of 222 patients) (10 missing values) (Table 3). Among these 113 patients, 80 (36.0% of 222 patients) had ≥ 6 swollen joints and 66 (29.7% of 222 patients) had ≥ 6 swollen and tender joints (Table 5).

Overall, 79 patients (34.1% of all patients) had ≥ 6 swollen joints and ≥ 6 tender joints, as well as either morning stiffness ≥ 45 min or an ESR ≥ 28. Forty-two patients (18.3% of 229 patients) had ≥ 6 swollen joints and ≥ 6 tender joints, as well as both morning stiffness ≥ 45 min and an ESR ≥ 28 (Table 5).

Analyses according to remission criteria for RA. In Cohort L, 30 of the 146 patients (20.5%) had no swollen joints, 43 (29.5%) no tender joints, 104 (72.2%) had normal ESR, 56 (38.4%) had morning stiffness ≤ 15 min, 35 (24.0%) had pain score ≤ 1.0, and 37 (25.3%) fatigue score ≤ 1 (Table 6). Among the 146 patients, 6 (4.1%) met the ACR remission criteria, with no swollen or tender joints, normal ESR, morning stiffness ≤ 15 min, pain score ≤ 1.0, and fatigue score ≤ 1.0.

In Cohort E, among the 232 patients, on a 42 joint count, 15 (6.5%) had no swollen joints, 32 (13.8%) no tender joints, 116 (51.1% of 227 patients) had normal ESR, 80 (36.0% of 222 patients) had morning stiffness ≤ 15 min, 32 (13.8%) had pain score ≤ 1.0, and 40 (17.2%) fatigue score ≤ 1 (Table 6). None of the 232 patients met all 6 ACR criteria for remission.

Analyses according to DMARD and biological therapy. All patients in Cohort L and 95.3% of patients in Cohort E were taking a DMARD, biological agent, or prednisone (Table 7).

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Table 4. Number (%) of 146 established patients with RA over 6.2 years (Cohort L) who met various inclusion criteria as candidates to participate in a clinical trial.

28 Joint Count	Total (%)	+ ESR ≥ 28 (%)	Morning Stiffness ≥ 45 min (%)
≥ 6 Swollen joints	62 (42.5)	21 (14.6)	33 (22.6)
≥ 6 Tender joints	37 (25.3)	11 (7.6)	24 (16.4)
ESR ≥ 28	36 (25.0)	NA	21 (14.6)
Morning stiffness ≥ 45 min	67 (45.9)	21 (14.6)	NA
≥ 6 Swollen joints + ≥ 6 tender joints	29 (19.9)	10 (6.9)	20 (13.7)
≥ 6 Swollen joints + ≥ 6 tender joints + Morning stiffness ≥ 45 min or ESR ≥ 28	22 (15.3)	NA	NA
≥ 6 Swollen joints + ≥ 6 tender joints + Morning stiffness ≥ 45 min and ESR ≥ 28	8 (5.6)	NA	NA

NA: Not applicable; ESR missing in 2 cases — the applicable number of patients is used in calculations of percentages.

Table 5. Number (%) of 232 patients with recent onset RA (Cohort E) who met various inclusion criteria as candidates to participate in a clinical trial.

42 Joint Count	Total (%)	+ ESR ≥ 28 (%)	Morning Stiffness ≥ 45 min (%)
≥ 6 Swollen joints	147 (63.4)	82 (36.1)	80 (36.0)
≥ 6 Tender joints	117 (50.4)	63 (27.8)	81 (36.5)
ESR ≥ 28	112 (49.3)	NA	56 (25.8)
Morning stiffness ≥ 45 min	113 (50.9)	56 (25.8)	NA
≥ 6 Swollen joints + ≥ 6 tender joints	90 (38.8)	56 (24.7)	66 (29.7)
≥ 6 Swollen joints + ≥ 6 tender joints + Morning stiffness ≥ 45 min or ESR ≥ 28	79 (34.1)	NA	NA
≥ 6 Swollen joints + ≥ 6 tender joints + Morning stiffness ≥ 45 min and ESR ≥ 28	42 (18.3)	NA	NA

NA: Not Applicable; ESR was missing in 5 cases, and morning stiffness in 10 cases — the applicable number of patients is used in calculations of percentages.

Table 6. Percentage of patients who met remission criteria, in 2 cohorts of 146 and 232 patients with RA seen in routine clinical care.

Measure	Cohort L	Cohort E
Number of patients	146	232
No swollen joints (0–28), %	20.5	10.7
No swollen joints (0–42)		6.5
No tender joints (0–28), %	29.5	20.3
No tender joints (0–42)		13.8
Normal ESR, %	72.2	51.1
Morning stiffness ≤ 15 min	38.4	36.0
No pain (≤ 1 on 0–10 VAS), %	24.0	13.8
No fatigue (≤ 1 on 0–10 VAS), %	25.3	17.2
Meet remission criteria, %	4.1	0

Table 7. Percentage of patients taking DMARD in 2 cohorts of 146 and 232 patients with RA seen in routine clinical care.

DMARD	No. (%) of Patients	
	Cohort L	Cohort E
MTX only	66 (45.2)	130 (56.0)
MTX + LEF/TNF-α inhibitor	30 (20.5)	39 (16.8)
MTX + traditional DMARD	30 (20.5)	16 (6.9)
LEF/TNF-α inhibitor only	3 (2.1)	20 (8.6)
Traditional DMARD only	11 (7.5)	6 (2.6)
Prednisone only	6 (4.1)	10 (4.3)

DMARD: disease modifying antirheumatic drug; MTX: methotrexate, LEF: leflunomide; TNF: tumor necrosis factor.

Most of these patients were taking MTX, including 86.2% in Cohort L and 79.7% in Cohort E. In addition, 22.6% of patients in Cohort L and 25.4% of patients in Cohort E were taking leflunomide or a tumor necrosis factor-α (TNF-α) inhibitor (Table 7). Clinical and demographic measures in patients in Cohorts L and E who were taking leflunomide or TNF-α inhibitors did not differ significantly from patients in these cohorts who were not taking these new agents, except in age in Cohort L and age and duration of disease in Cohort E (data not shown).

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Table 8. Percentage of 146 patients with established RA with mean duration of 14 years (Cohort L) who met various inclusion criteria (on a 28 joint count) as candidates to participate in a clinical trial, according to current therapies.

DMARD	No. (%) of Patients	SJC ≥ 6, %	TJC ≥ 6, %	ESR ≥ 28, %	AM ≥ 45, %	SJC ≥ 6 + TJC ≥ 6 + ESR ≥ 28 or AM ≥ 45, %	SJC ≥ 6 + TJC ≥ 6 + ESR ≥ 28 and AM ≥ 45, %
MTX only	66 (45.2)	40.9	24.2	30.3	45.5	15.2	4.5
LEF/TNF-α only or with MTX	33 (22.6)	36.4	27.3	18.8	51.5	15.2	3.0
MTX with traditional DMARD	30 (20.5)	43.3	13.3	20.7	30.0	3.4	3.3
Traditional DMARD only or prednisone only	17 (11.6)	58.8	47.1	23.5	64.7	35.3	17.6
Total	146 (100)	42.5	25.3	25.0	45.9	15.3	5.6

DMARD: disease modifying antirheumatic drug, SJC: swollen joint count, TJC: tender joint count, ESR: erythrocyte sedimentation rate, AM: morning stiffness, MTX: methotrexate, LEF: leflunomide, TNF: tumor necrosis factor inhibitor.

Table 9. Percentage of 232 patients with early RA (Cohort E) who met various inclusion criteria (on a 42 joint count) as candidates to participate in a clinical trial, according to current therapies.

DMARD	No. (%) of Patients	SJC ≥ 6, %	TJC ≥ 6, %	ESR ≥ 28, %	AM ≥ 45, %	SJC ≥ 6 + TJC ≥ 6 + ESR ≥ 28 or AM ≥ 45, %	SJC ≥ 6 + TJC ≥ 6 + ESR ≥ 28 and AM ≥ 45, %
MTX only	130 (56.0)	60.8	45.4	48.0	49.6	31.5	14.8
LEF/TNF-α only or with MTX	59 (25.4)	64.4	59.3	49.2	48.3	33.9	22.0
MTX with traditional DMARD	16 (6.9)	75.0	50.0	50.0	56.3	43.8	25.0
Traditional DMARD only or prednisone only	16 (6.9)	54.5	56.3	71.4	60.0	43.8	26.7
No DMARD or prednisone	11 (4.7)	54.5	54.5	36.4	60.0	36.4	18.2
Total	232 (100)	63.4	50.4	49.3	50.9	34.1	18.3

DMARD: disease modifying antirheumatic drug, SJC: swollen joint count, TJC: tender joint count, ESR: erythrocyte sedimentation rate, AM: morning stiffness, MTX: methotrexate, LEF: leflunomide, TNF: tumor necrosis factor inhibitor.

The 4 major criteria for inclusion in clinical trials were analyzed in patients in 4 categories according to current therapies in Cohort L (Table 8) and Cohort E (Table 9): MTX only; leflunomide and/or TNF-α inhibitors with or without MTX (< 10% without MTX); MTX with a traditional DMARD; and traditional DMARD or prednisone. Cohort L patients who were not taking MTX had a higher likelihood of meeting the 4 criteria for clinical trials than patients who were taking MTX, leflunomide, or a TNF-α inhibitor (Table 8) ($p = 0.038$ for patients who had ≥ 6 swollen joints and ≥ 6 tender joints, and either morning stiffness ≥ 45 min or an ESR ≥ 28; all other comparisons $p > 0.05$). A similar trend was seen for ESR and morning stiffness in Cohort E (Table 9), although no differences were statistically significant (all comparisons $p > 0.05$). Nonetheless, only 35.3% of Cohort L patients and 43.8% of Cohort E patients who took traditional DMARD or prednisone only had ≥ 6 swollen joints and ≥ 6 tender joints, and either morning stiffness ≥ 45 min or an ESR ≥ 28.

DISCUSSION

Data presented in this report indicate that only about half or fewer patients seen in 2 rheumatology clinical care settings met any of 4 inclusion criteria in many clinical trials in RA (Table 1) (that is, ≥ 6 swollen joints, ≥ 6 tender joints, ESR ≥ 28, or morning stiffness ≥ 45 min) other than 63.4% of the recent-onset patients having ≥ 6 swollen joints. These 4 measures have been used as inclusion criteria in almost all clinical trials sponsored by pharmaceutical companies over the last decade to introduce new drugs or biological agents. The criteria of ≥ 6 swollen and tender joints as well as an ESR ≥ 28 or morning stiffness ≥ 45 min were met by 15.3% of patients in Cohort L of 146 patients with established RA, and 34.1% of patients in Cohort E of patients with recent-onset RA.

The inclusion criteria of 6 or more swollen and/or tender joints in clinical trials in patients with RA was appropriate in earlier decades when drug therapy was not as effective as it is at this time. However, with recognition of the severity

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of RA and a need for aggressive intervention with DMARD[32-39], these inclusion criteria may no longer be optimal or even desirable in development of new therapies, DMARD, and biological agents often used in combinations[45]. Although therapies for RA have changed considerably over the last 2 decades, criteria for inclusion in clinical trials have not changed.

The inclusion criterion of an ESR of 28 or more was met by only 25% of patients at the study visit in Cohort L, and by 49.3% of patients in Cohort E. It is recognized that up to 40% of patients have a normal ESR at their first visit[46], and the ESR tends to be stable over the longterm course of RA[47]. Only 6.9% of patients in Cohort L and 24.7% of patients in Cohort E had ≥ 6 swollen joints, ≥ 6 tender joints, and an ESR ≥ 28. Therefore, a requirement for an ESR ≥ 28 excludes many patients with active RA from clinical trials.

The inclusion criterion of morning stiffness ≥ 45 minutes was met by 45.9% of patients in Cohort L, and by 50.9% of patients in Cohort E. This criterion would allow inclusion of more patients when used as an alternative to an ESR ≥ 28, 15.3% of Cohort L and 34.1% of Cohort E. Nonetheless, fewer than 35% of the patients in either of these 2 cohorts would meet inclusion criteria for a clinical trial at the time of study visit.

One possible explanation for patients with RA not meeting inclusion criteria for clinical trials might be that they were taking aggressive therapy. Indeed, more than 70% of the patients took MTX, with or without traditional DMARD, and about 25% took leflunomide or a TNF-α inhibitor. However, only 35.3% of Cohort L patients and 43.8% of Cohort E patients who took no MTX had ≥ 6 swollen joints and ≥ 6 tender joints, and either morning stiffness ≥ 45 min or an ESR ≥ 28. Patients who were taking MTX were as likely to be ineligible for clinical trials as patients who took leflunomide or a TNF-α inhibitor.

If our findings are generalizable to reflect current state-of-the-art therapy, a majority of patients are not eligible to be included in clinical trials of further new drugs. It may appear desirable that patients "flare" to meet inclusion criteria to study the efficacy criteria for a new drug, but this may be neither ethical nor desirable to identify new therapies for RA. A need to flare from recognized therapy would suggest either that there may be no need for the new drug or that findings from clinical trials will pertain to a very small minority of patients.

Another possible explanation for many patients with RA not meeting inclusion criteria for clinical trials might be that they were in remission. However, only 6 patients in Cohort L and no patient in Cohort E met the 6 ACR criteria for remission. Therefore, most patients seen in both cohorts met neither criteria for remission nor criteria for inclusion in most contemporary clinical trials. It is possible that further development of optimal therapeutic goals may involve a definition of a "target value" of therapy, as sometimes seen in management of diabetes or hypertension, rather than criteria for remission or a percentage improvement[48].

Several limitations are seen in this study. First, an index of 28 or 42 joints will identify fewer tender and/or swollen joints than an index of 66 swollen or 68 tender joints, as used in many studies. However, the 28 joint count includes all 10 joints that are abnormal in more than 30% of patients and the 42 joint count identifies all 17 joints abnormal in 20% or more of patients[44]. Inclusion of joints that are abnormal in a small number of patients ironically may dilute the sensitivity of this measure to detect changes[44,49-52], and the number of patients who might meet ACR 20, 50, and 70 responses[53] may likely be reduced[54]. Second, the patients are from only 2 clinical care settings in which aggressive therapy is the practice; a greater proportion of patients in other clinical settings may have greater disease severity. A third limitation to Cohort L is that most patients had established disease with long-standing clinical care. However, these patients represent a population from which a clinician would seek to enroll into a typical clinical trial of a new agent, and the results are in the main comparable to those seen in new onset patients in 2001. Further, the analyses presented indicate a maximum possible number of patients eligible for clinical trials according to 4 common inclusion criteria, as additional inclusion and exclusion criteria would inevitably reduce the number of eligible patients. Therefore, the data overestimate the actual number of eligible patients.

It is recognized that partial control of inflammation may not necessarily prevent longterm joint damage[55-61]. Therefore, an important question for rheumatologists is whether the 66.3% of patients in Cohort L and 57.8% of patients in Cohort E who have 1–5 swollen joints and/or tender joints should be candidates for new therapies such as leflunomide, etanercept, infliximab, or anakinra. No data from formal clinical trials performed to date (or in progress, to the best knowledge of the authors) are available to answer this question. It may be in the interest of pharmaceutical companies as well as patients to consider conducting clinical trials in patients with fewer than 6 swollen or tender joints, and possibly even with a normal ESR, who are the majority of patients in these cohorts.

It may appear superficially preferable that patients included in clinical trials of new RA therapies have as many affected joints as possible at baseline to document treatment efficacy. This view may be valid statistically, but it may not be clinically valid, at least in certain patients, particularly with long duration of disease. Some patients who have high numbers of swollen joints while taking MTX in contemporary clinical care may be more refractory to all therapies than most patients with RA, and may not be as likely to respond to any therapy. By contrast, some patients who have only a few swollen joints while taking MTX may, ironically, be more likely to have additional responses to additional drugs. No data are available concerning this matter, but

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further information comparing responses of patients according to the number of swollen or tender joints, including fewer than 6 swollen or tender joints, would appear to be of considerable interest.

The primary goal of this report is to recognize that many patients in contemporary rheumatologic care do not meet criteria for inclusion in clinical trials of new agents for RA. We do not suggest that all patients with RA seen in a clinical setting should necessarily be candidates for clinical trials. For example, the 13% of patients in Cohort L and 6.5% in Cohort E who had no swollen or tender joints would probably not be candidates for any type of studies of new therapies. Further, this report is not directed to present proposed possible revisions for eligibility of patients in future RA clinical trials. Nonetheless, it may be an important problem for the rheumatology community if the majority of patients seen in usual clinical care are neither eligible for most clinical trials of new agents nor in remission. It would appear worthwhile to reexamine inclusion criteria for current clinical trials (and possibly remission criteria as well) for the benefit of rheumatologists, pharmaceutical companies, and above all, people with RA.

ACKNOWLEDGMENT

The authors 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 this study; Melissa Gibson and Christopher Swearingen for helpful technical assistance; and Drs. Pekka Hannonen, Anthony Russell, and Arja Häkkinen for helpful editorial suggestions.

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