Patient Retention and Hand-Wrist Radiograph Progression of Rheumatoid Arthritis During a 3-Year Prospective Study That Prohibited Disease Modifying Antirheumatic Drugs

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ABSTRACT. ***Objective.*** To quantitate patient retention and radiographic progression rates in serial hand/wrist radiographs of patients with rheumatoid arthritis (RA) who were not being treated with disease modifying antirheumatic drugs (DMARD).

Methods. A total of 1433 RA patients with 1–7 years' disease duration entered a 3-year prospective randomized double-blind clinical trial comparing the nonsteroidal antiiflammatory drugs (NSAID) etodolac (300 or 1000 mg daily) and ibuprofen (2400 mg daily). Standardized hand/wrist radiographs were obtained yearly and at dropout if > 6 months after entry. DMARD were not permitted. Joint erosion, joint space narrowing (JSN), and total scores of 3 readers were averaged.

Results. At entry, mean duration of RA was 3.5 years (range 1–7); ages were 21–78 years; patients were 71% female, 84% Caucasian, 67% rheumatoid factor (RF) positive; tender joint count was 29, swollen joint count 22, Westergren erythrocyte sedimentation rate (ESR) 49, and C-reactive protein (CRP) 2.44. There were 824 (57.5%) patients who completed ≥ 6 months and had paired radiographs; 46% completed 48 weeks; 31%, 98 weeks; and 19%, 147 weeks. Months between paired radiographs (time in study) averaged 23.1 (range 6–36). Mean progression rates for total, erosion, and JSN scores (5.08, 2.53, and 2.54 units per year, respectively) were significantly associated with time in study, baseline RF, ESR, CRP, swollen joint count, presence of erosions at entry, and with 20% and 50% composite clinical responses. Painful joint count and RA duration were weakly associated only with progression of erosions. Progression rates were not associated with age, sex, corticosteroid use, or prior DMARD use. Patients who completed the 3-year trial had less severe disease activity and radiographic progression than those who dropped out.

Conclusion. In this 3-year prospective double-blind clinical trial that prohibited DMARD, retention rates (57.5%, 46%, 31%, and 19% at 0.5, 1, 2, and 3 years) were similar to those in the non-DMARD-treated placebo groups of recent published studies. Radiographic progression rates are reported for 824 non-DMARD-treated patients during RA of 1–10 years' duration. This information may be useful as background information in the interpretation of longterm clinical trials that evaluate joint radiographic outcomes. (J Rheumatol 2004;31:470–81)

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RHEUMATOID ARTHRITIS RADIOGRAPHIC PROGRESSION

The 1999 revision of the US Food and Drug Administration (FDA) guidelines for clinical development of antirheumatic therapies[1] for rheumatoid arthritis (RA) includes potential claims for prevention of structural damage (for ≥ 1 year) and for prevention of disability (sustained improvement of physical function for ≥ 2 years). This has stimulated the inclusion of joint radiographic outcomes in clinical trials of new disease modifying antirheumatic drugs (DMARD) such as recent clinical trials of leflunomide[2-4], an interleukin 1 receptor antagonist (IL-1ra)[5,6], and tumor necrosis factor inhibitors[7,8], as well as attempts to design and conduct adequately controlled double-blind prospective clinical

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trials with durations ≥ 2 years. It is logical to require that treatments that claim to control RA demonstrate such control for a meaningful fraction of this lifelong chronic disease. However, even if the candidate treatment provides longterm control for most patients and background nonsteroidal antiiflammatory drug (NSAID) and corticosteroid treatment is continued for all patients, attrition from a placebo or alternative-treated control group creates major analytic problems due to the large amount of missing data (from dropouts) in the later phases of a 2 to 5 year study. Quantitative information about patient retention and radiographic changes that occurred during a prospective double-blind controlled clinical trial in patients who were not being treated with DMARD would be useful to describe the risk factors for radiographic progression, and as background information for the evaluation of reports of clinical trials that use radiographic outcome measures.

Several methods for assessing radiographic progression have evolved from the FDA Guidance Document[1] as it was applied to the leflunomide trials[2-4]: (1) The cumulative scores of erosions and joint space narrowing (JSN) of specified joints of the hands/wrists and forefeet. (2) Enumeration of patients with no newly eroded joints, i.e., no joint that was not eroded at baseline has become eroded at the followup evaluation. This definition permits an increase in the cumulative erosion score, provided the increase occurs only in previously eroded joints. (3) In a stricter version, patients with no increase in erosion score in any joint are enumerated, i.e., no increase in erosions in previously eroded joints or in previously non-eroded joints is allowed.

This report describes patient retention and progression of structural damage of hand/wrist radiographs during a 3-year prospective double-blind comparison of 2 doses of etodolac with ibuprofen in which patients were permitted to continue prestudy low dose prednisone, but were not allowed DMARD for 6 months before and during the study. Thus, the treatment of all patients in this study was similar to that of the placebo-control patients in current studies of DMARD. The study was done between 1984 and 1989, when aggressive use of DMARD in early RA was not yet the standard of care, but randomization to prolonged non-DMARD treatment is no longer likely to be acceptable unless provision is made for early withdrawal for lack of benefit. In addition, for the purpose of analysis and comparison, we review patient retention and radiographic progression in the placebo-control groups of some recent published studies.

MATERIALS AND METHODS

Clinical trial. The clinical trial was sponsored by Wyeth-Ayerst Research and conducted by 97 clinical investigators. The 1433 enrolled patients satisfied American Rheumatism Association (ARA) criteria for RA[9], were Steinbrocker Stage I (39%) or II (61%)[10] and functional class I (22%) or II (76%)[9], had disease duration between 1 and 7 years, and met specified RA activity and flare criteria when withdrawn from prestudy NSAID. No other NSAID or DMARD were permitted during the trial, and patients were ineligible if they had taken any DMARD during the 6 months before study entry. Patients taking a stable dose of not more than 5 mg per day prednisone were eligible; the entry prednisone dose could not be increased during the trial, but could be decreased at the discretion of the investigator; 328 patients continued a mean dose of 4.41 mg prednisone daily. Seventy-one percent of the patients were female and 84% Caucasian, with average age 53 ± 11 (SD) years and 3.5 ± 1.9 years disease duration. All patients provided written informed consent, and the protocol was approved by the appropriate institutional review boards.

In all, 614 patients were randomized to etodolac 150 mg twice a day, 405 to etodolac 500 mg twice a day, and 414 to ibuprofen 600 mg four times a day. Blister packs contained 4 identical-appearing doses for each day, with instructions indicating the time of day for each dose. For patients assigned to etodolac, some of the capsules were placebo, with enough etodolac capsules to produce the assigned dosage schedule. Patients were evaluated every 2 weeks for the first 4 months, then monthly for 2 months, every 8 weeks for 6 months, and every 12 weeks for the remaining 2 years. Evaluations[11] included counts and scores (0 to 3 for each joint) of 68 joints for pain/tenderness and 66 joints for swelling, duration of morning stiffness, grip strength using a folded sphygmomanometer cuff, time required to walk 50 feet, investigators' and patients' opinions of patients' disease condition on the day of assessment (1 to 5 scale), intensity of joint pain (1 to 5 scale) and time to onset of fatigue. Also included were ARA functional class (I to IV)[10], Steinbrocker progression stage (I to IV)[10],Westergren erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and rheumatoid factor (RF). Routine laboratory and clinical safety assessments were done at each visit.

Using high resolution, single screen/single emulsion film, standard posteroanterior radiographs of hands and wrists were scheduled at entry and yearly during the trial, and at time of withdrawal if the patient had taken medication for at least 6 months and if it had been more than 3 months since the last radiographs. The 824 patients with paired radiographs are the basis for this report. For each patient, the baseline and last available radiographs were scored by 3 experienced readers for erosions and JSN; total score is the sum of the erosion and JSN scores. After a brief "training" session in which the readers discussed the scoring scale and reviewed a small group of radiographs to be sure that they agreed on the features to be scored, the radiographs were independently scored by the 3 readers. Radiographs were read in patient sets, blinded and randomized for sequence and treatment. One reader used the method described in Sharp, *et al*[12,13] to score 14 joints of each hand and wrist for erosions [5 proximal interphalangeal (PIP), 5 metacarpophalangeal (MCP), ulna, radius, navicular, and first carpal-metacarpal joints] and 13 for JSN (5 PIP, 5 MCP, radio-carpal, carpal-navicular-lunate, and 5th carpal-metacarpal joint spaces). The other 2 readers used the method described by Genant, *et al*[6,14,15], and scored the same joints[15]. JSN was scored on the same 0 to 4 scale by all readers[12-15]. For the statistical analyses, erosion scores were converted to a 0–5 scale[13] as follows:

Standardized Score	Method 1 (H. Genant, B. Weissman)	Method 2 (J. Sharp)
0	Normal (0) or Questionable (+)	Normal (0) or Questionable (+)
1	Mild (1)	One erosion or area (1)
2	Worse than mild (1+)	Two erosions or areas (2)
3	Moderate (2)	Three erosions or areas (3)
4	Worse than moderate (2+)	Four erosions or areas (4)
5	Severe (3), or Worse (3+)	Destruction of half of one articulating surface (5) or Worse (5+)

Maximum possible scores were erosions 140 and JSN 104, and total score

244. The standardized scores of the 3 readers for each radiograph were averaged and this average was used for the analysis[16]. To determine "baseline radiographic score of zero" for each set of films, a score of 0.33 (one reader scored 1; 2 readers scored zero) is considered to be zero; scores of 0.66 are considered to be 1. To measure interrater reliability among readers, Cronbach's alpha was calculated for 1, 2 and 3 year change scores; calculated alpha values were 0.89 to 0.93 for erosion and 0.87 to 0.91 for JSN scores. Sclerosis or healing of erosions was not evaluated. Because the time interval between pairs of radiographs varied among patients, radiographic progression was determined by dividing the difference between the scores of each pair of radiographs by the months elapsed between the radiographs; the progression rate for each patient was expressed as change in (total, erosion, or JSN) score per month; this was annualized when necessary to express progression rate per year.

Following the initial pre-baseline NSAID withdrawal flare, all treatment groups improved clinically. Response rates from the NSAID withdrawal flare (baseline) to the last recorded observation were calculated using the composite criteria described by Paulus, *et al*[17], which require ≥ 20% improvement in ≥ 4 of the following 6 criteria: tender joint score (68 joints), swollen joint score (66 joints), patient and physician global opinion of RA severity, duration of morning stiffness, and acute phase reactant (ESR or CRP). One patient with a baseline erosion score of 158 was considered an outlier and excluded from this analysis. In this report no corrections or extrapolations are made to compensate for patient withdrawals, and no sensitivity analyses were done.

Continuous variables were analyzed by 2-way analysis of variance, qualitative or categorical variables by chi-square or Fisher's exact test, and relationships among variables by correlation and regression analysis. Analysis of covariance (ANCOVA) was used to adjust for baseline differences between the groups. The data distribution was decidedly non-normal and skewed. Both parametric and nonparametric tests were done and led to similar conclusions. The results of the parametric (ANCOVA) testing are presented here. Formal Bonferroni correction was not done. For the descriptive subgroup analyses, the 3 NSAID groups were pooled. The following subgroups were examined: time in study 6 to 12 mo, 13 to 24 mo, 25 to 35 mo, 36 mo; RA duration 12 to 24 mo, 25 to 48 mo, 49 to 84 mo; age < 40, 40 to 60, > 60 yrs; sex; RF at baseline; ESR at baseline; tender and swollen joint counts at baseline; corticosteroid use; composite clinical response; patients with baseline radiographic total score of zero; patients with no increase in erosion score; patients with no newly eroded joints.

For comparison with published studies, standardized response means (SRM) for radiographic progression were calculated as follows. For each patient the change score was calculated by subtracting the baseline (total, erosion, or JSN) score from the score of the last available radiograph and dividing by the number of months between the pairs of radiographs. Population means and standard deviations of monthly progression rates were calculated. SRM[18,19] for the monthly progression rate is the mean progression rate per month divided by its standard deviation (SD). SRM is a unitless measure, similar but not identical to effect size. Cohen[18] classifies effect sizes as small (< 0.5), medium (0.5–0.8), or large (> 0.8).

SRM sizes for the published studies[2,4,5,20-22] were calculated as the reported mean change during the study divided by the SD of this change. The SD was not stated in the study by Hannonen, *et al*[20]; however, the mean change and complete range of change values were given; to estimate SD, the range was divided by 6 (i.e., ± 3 SD).

RESULTS

Demographic data are presented in Table 1. At study entry, the patients with paired radiographs were representative of the entire study population. The subgroup with baseline total radiographic score of zero were younger, heavier, more likely to be RF negative, had lower ESR and CRP values and lower swollen joint counts, and were less likely to have had prior DMARD treatment. The swollen and tender joint counts, ESR, and global assessments confirmed that the entry criteria succeeded in selecting patients with extensive active RA. Between study entry and exit visits, 4 or more of the 6 composite criteria improved by at least 20%[17] in half of all (1433) patients and in 65% of the 824 patients with paired radiographs; more stringent 50% responses (≥ 50% improvement in ≥ 4 criteria) were achieved by 28% of all patients and 41% of patients with paired radiographs, suggesting that patients who remained in the study long enough to get the second radiographs (6 months or longer) had better clinical responses than those who dropped out before 6 months. Among the 1433 patients, there were 33 remissions by ARA proposed criteria for clinical remission in RA[23]; 2.6% of etodolac 300 mg, 2.4% of etodolac 1000 mg, and 1.7% of ibuprofen 2400 mg patients.

Table 2 describes the withdrawal rate for this trial in comparison with some other studies that used a non-DMARD comparison group. At 24 weeks, 57.5% of our patients remained, compared to 55% of the placebo group in the leflunomide/sulfasalazine[2] study, and 68% of the placebo group in the IL-1ra study[5], which required daily injections. At 48 weeks, 46% of our patients remained, compared with 26% continuing placebo in the leflunomide/MTX study[4], 27.5% of the placebo group in the sulfasalazine study[20], 73% of the placebo group in the minocycline study[22], and 38% of the placebo group in the cyclosporine study[21]. In the cyclosporine/placebo study[21], per protocol, all patients took prednisolone 15 mg daily for the first 6 weeks, tapered to 7.5 mg at 10 weeks and to 3.75 mg daily maintenance after 16 weeks; despite the mandated background prednisolone, 57% of the placebo patients withdrew for lack of efficacy, at which time their average prednisolone dose was 7.9 mg/day. Thirty-one percent and 19% of our patients remained after 98 and 147 weeks, respectively.

By the 24th week, 317 patients (22.1%) had withdrawn because of lack of efficacy. Overall during the entire 3-year study, 39% withdrew because of insufficient efficacy, 13% for an adverse reaction or abnormal laboratory values, 17% for other reasons (lost to followup, protocol violations, moved, etc), and 12% were prematurely discontinued when the sponsor decided to stop the study. Comparing the etodolac and ibuprofen treatment groups, there were no significant differences in any of the baseline characteristics listed in Table 1 (data not shown). Hand-wrist radiographic erosion, JSN, and total score progression rates per month for each of the 3 treatment groups were compared, and were significantly different for only one of the 9 possible comparisons (etodolac 300 mg/day erosion progression was significantly less than that of ibuprofen 2400 mg/day).

To prospectively describe radiographic progression during the 3-year study of non-DMARD-treated RA in these patients with 1 to 7 years' disease duration at entry to the study, the 3 NSAID groups were pooled and subgroups of

Table 1. Patient characteristics at study entry.

	All Patients, n = 1433	Patients with Paired Radiographs, n = 824	Patients with Paired Radiographs with Baseline Total Score 0, n = 81	≥ 1, n = 743
Age, yrs	52.7	52.7	45.6	53.5**,b
Female, %	71	71	68	71
Caucasian, %	84	84	75	85
African American, %	10	9.2	14	9
Weight, kg	74	74.1	79.7	73.4**, b
Duration of RA, yrs	3.5	3.5	3.3	3.5
Previous DMARD use, %	23	23.5	15	25*, a
Prednisone use (≤ 5 mg/day), %	22.9	23.9	20	24
RA abrupt onset, %	32	31	33	31
RA insidious onset, %	68	69	67	69
Tender joints (maximum 68)	28.69	29.19	26.9	29.4
Swollen joints (maximum 66)	21.57	21.77	18.1	22.1**, b
Patient global (1–5)	3.9	3.88	3.83	3.89
Physician global (1–5)	3.78	3.76	3.72	3.77
ESR, Westergren, mm/h	49.9	48.6	40.8	49.5**, c
CRP, mg/dl	2.44	2.24	1.22	2.35**, c
RF, IU	578	536	255	567**, c
RF negative, %	31	33	52	31**, a
Randomized distribution of drug assignments, %				
Etodolac 300 mg/day	43	44	45	44
Etodolac 1000 mg/day	28	27	19	27
Ibuprofen 2400 mg/day	29	29	35	28

* p = 0.051, ** p = < 0.001; a: chi-square, b: ANOVA, c: Wilcoxon.

Table 2. Trial profiles. Patient attrition in non-DMARD arms of prospective double-blind randomized clinical trials that included joint radiograph assessments. Data are percentage continuing assigned treatment.

Clinical Trial	Study Duration, Weeks	Baseline, n	24 Weeks, %	48 Weeks, %	98 Weeks, %	147 Weeks, %
Longterm etodolac trial						
Total	147	1433	57.5	46	31	19
Etodolac 300 mg/day		620	58	49	32	21
Etodolac 1000 mg/day		409	56	47	35	21
Ibuprofen 2400 mg/day		417	59	44	29	17
Placebo leflunomide/sulfasalazine[2]	24	92	55	—	—	—
Placebo leflunomide/MTX[4]	48	118	—	26	—	—
Placebo sulfasalazine[20]	48	40	—	27.5	—	—
Placebo IL-1 ra injections[5]	24	121	68	—	—	—
Placebo minocycline[22]	48	110	—	73	—	—
Placebo cyclosporine plus prednisolone 15 mg/day tapering to 5.3 mg/day[21]	48	61	—	38	—	—

the 824 patients with paired radiographs were analyzed (Tables 3A, 3B, 3C). Examining total scores (Table 3A), the interval between the entry and final radiographs, i.e., time on study, was associated with a slower radiographic progression rate per month in the patients who completed 25 to 36 months of the study. Progression rates were not significantly related to the duration of RA at entry, age, sex, current corticosteroid use, history of prior DMARD use, or number of painful joints at entry. Baseline factors significantly associated with radiographic progression were RF positivity, ESR, and swollen joint count. The patients who had the best clinical responses (20% and 50% composite responses) had slower radiographic progression. The 81 patients with no radiographic damage (total score 0) at entry had very little change during the study, compared to those with scores ≥ 1 at baseline.

The findings with erosion and JSN scores (Tables 3B, 3C) are similar to those with total scores, except for weak associations of erosion progression rate with number of painful joints at entry (p = 0.036) and with RA duration (p = 0.030); this association is not present with JSN or total score progression rates.

Table 3A. Joint radiograph progression rates (mean ± SD). Total (erosion and narrowing) scores.

Comparisons	N	Baseline Score	Duration of RA, mo	Imputed Prestudy Progression Rate per Month	Last Visit Score	Change During Study	Months Elapsed	Progression Rate per Month During Study	p†	SRM
All with Paired Radiographs	824	20.7 ± 27.8	42 ± 23	0.560 ± 0.738	29.5 ± 34.0	8.7 ± 13.6	23.1	0.423 ± 0.658		0.64
Radiograph interval (entry to final film)										
Completed study	276	19.0 ± 26.5	43 ± 23	0.510 ± 0.699	29.6 ± 33.4	10.6 ± 15.4	34.4	0.313 ± 0.448		0.70
25–35 mo	164	20.3 ± 26.7	39 ± 22	0.644 ± 0.872	30.4 ± 33.9	10.1 ± 13.8	27.6	0.385 ± 0.543		0.71
13–24 mo	218	23.2 ± 30.7	42 ± 22	0.571 ± 0.735	32.1 ± 37.8	8.8 ± 14.2	16.7	0.545 ± 0.834	0.002	0.65
6–12 mo	166	20.9 ± 27.3	43 ± 24	0.548 ± 0.658	24.9 ± 29.5	4.0 ± 6.4	8.4	0.483 ± 0.756		0.64
RA duration at entry										
12–24 mo	252	11.5 ± 14.3	16 ± 3.7	0.538 ± 0.790	20.1 ± 21.8	8.6 ± 13.1	23.5	0.407 ± 0.572		0.71
25–48 mo	254	18.5 ± 26.3	36 ± 7	0.714 ± 0.882	27.8 ± 34.2	9.3 ± 14.6	23.4	0.433 ± 0.684	0.109	0.63
49–84 mo	318	29.9 ± 33.8	67 ± 12	0.457 ± 0.523	38.3 ± 39.4	8.4 ± 13.1	22.6	0.428 ± 0.700		0.61
Ages										
> 60 yrs	231	28.2 ± 31.5	43.2 ± 23.6	0.754 ± 0.862	36.1 ± 36.3	7.9 ± 11.9	23.3	0.405 ± 0.637		0.64
40–60 yrs	487	18.9 ± 27.0**	42.5 ± 22.8	0.500 ± 0.656	27.8 ± 33.9	8.9 ± 14.1	23.1	0.427 ± 0.671		0.64
< 40 yrs	106	12.7 ± 17.6	36.3 ± 21.8	0.416 ± 0.729	22.7 ± 26.4	9.6 ± 14.4	22.9	0.445 ± 0.644	0.1	0.69
Sex										
Male	241	17.8 ± 24.3	39.4 ± 23.7	0.494 ± 0.616	26.2 ± 30.2	8.4 ± 12.6	23.9	0.371 ± 0.559	0.339	0.66
Female	583	22.0 ± 29.1	42.9 ± 22.6	0.588 ± 0.782	30.8 ± 35.4	8.9 ± 13.9	22.8	0.445 ± 0.694		0.64
Corticosteroid use										
No prednisone	627	18.8 ± 26.8**	41 ± 23	0.534 ± 0.762	27.3 ± 33.2	9.5 ± 12.6	23.3	0.411 ± 0.649	0.941	0.63
Prednisone	197	26.8 ± 30.2	43 ± 24	0.643 ± 0.651	36.4 ± 35.7	8.5 ± 13.7	22.5	0.460 ± 0.686		0.67
Prior DMARD use										
No	630	16.3 ± 23.9**	38.1 ± 22.0	0.523 ± 0.764	24.8 ± 30.4	8.5 ± 13.4	23.6	0.407 ± 0.622		0.65
Yes	194	35.2 ± 34.1	53.9 ± 21.4	0.682 ± 0.636	44.6 ± 40.4	9.3 ± 14.0	21.5	0.476 ± 0.762	0.261	0.62
Rheumatoid factor										
Negative, ≤ 60 IU	272	13.3 ± 20.8	42.2 ± 24.2	0.390 ± 0.602	17.3 ± 26.1	4.0 ± 9.7	24.6	0.166 ± 0.376	< 0.001	0.44
Positive	552	24.4 ± 30.1**	41.7 ± 22.4	0.644 ± 0.784	35.5 ± 35.6	11.1 ± 14.5	22.4	0.55 ± 0.727		0.77
61–187	182	21.3 ± 27.7	42 ± 22	0.541 ± 0.610	29.4 ± 31.4	8.2 ± 11.5	23.7	0.384 ± 0.533		0.72
188–640	183	25.2 ± 30.9	41 ± 23	0.683 ± 0.864	37.6 ± 37.1	12.4 ± 14.6	21.4	0.620 ± 0.741		0.84
> 640	187	26.6 ± 31.3	42 ± 24	0.707 ± 0.844	39.3 ± 38.1	12.6 ± 16.3	22.0	0.642 ± 0.842		0.76
ESR at baseline										
≤ 30	93	12.2 ± 18.5	40.5 ± 24.3	0.376 ± 0.534	17.9 ± 23.5	5.8 ± 9.7	22.4	0.247 ± 0.371	< 0.001	0.67
31–50	434	18.7 ± 25.3**	42.5 ± 22.9	0.484 ± 0.597	26.6 ± 31.7	7.9 ± 13.0	23.9	0.357 ± 0.565		0.63
> 50	295	26.5 ± 32.5	41.7 ± 22.6	0.725 ± 0.924	37.4 ± 38.3	10.9 ± 15.1	22.3	0.574 ± 0.811		0.76
CRP at baseline										
≤ 0.60 (negative)	212	12.4 ± 21.0	41.8 ± 23.4	0.383 ± 0.678	16.5 ± 24.5	4.1 ± 8.8	24.9	0.182 ± 0.412	< 0.001	0.44
0.61–1.34	211	15.6 ± 22.2**	41.5 ± 22.9	0.407 ± 0.516	22.0 ± 27.6	6.4 ± 10.6	23.2	0.284 ± 0.439		0.65
1.35–3.28	215	25.6 ± 30.9	41.7 ± 22.6	0.684 ± 0.825	35.9 ± 35.8	10.4 ± 13.0	22.5	0.518 ± 0.675		0.77
> 3.28	185	30.6 ± 32.4	42.3 ± 23.1	0.796 ± 0.824	45.6 ± 39.6	14.8 ± 18.3	21.7	0.749 ± 0.886		0.85
Painful joints, n										
0–21	266	16.9 ± 25.8	42.8 ± 23.8	0.444 ± 0.660	23.4 ± 29.4	6.5 ± 9.4	22.5	0.327 ± 0.508		0.64
22–33	281	20.5 ± 26.4**	41.5 ± 22.5	0.545 ± 0.667	28.8 ± 32.0	8.4 ± 12.7	23	0.417 ± 0.627	0.34	0.67
34–68	275	24.8 ± 30.6	41.6 ± 22.6	0.683 ± 0.850	36.1 ± 38.9	11.3 ± 17.0	23.9	0.520 ± 0.793		0.66
Swollen joints, n										
0–15	273	17.3 ± 26.2	42.0 ± 23.6	0.482 ± 0.761	23.6 ± 31.2	6.3 ± 10.3	23.1	0.299 ± 0.440	0.002	0.68
16–25	263	18.5 ± 25.1**	41.0 ± 22.6	0.523 ± 0.680	27.3 ± 30.4	8.7 ± 12.8	23.3	0.420 ± 0.658		0.64
26–66	286	26.1 ± 31.0	42.9 ± 22.7	0.664 ± 0.753	37.2 ± 38.3	11.1 ± 16.4	23	0.543 ± 0.798		0.68
20% composite responses										
Responders	536	19.1 ± 26.6**	40.7 ± 22.9	0.541 ± 0.753	27.2 ± 32.6	8.1 ± 13.4	25.6	0.340 ± 0.566		0.60
Nonresponders	288	23.7 ± 29.9	44.2 ± 22.9	0.597 ± 0.711	33.7 ± 36.2	10.0 ± 13.8	18.5	0.578 ± 0.779	< 0.001	0.74
50% composite responses										
Responders	335	16.1 ± 23.7**	40.7 ± 23.4	0.456 ± 0.670	22.3 ± 28.5	6.2 ± 10.9	27.2	0.237 ± 0.402		0.59
Nonresponders	489	23.9 ± 29.9	42.7 ± 22.7	0.632 ± 0.774	34.4 ± 36.5	10.5 ± 14.6	20.3	0.551 ± 0.761	< 0.001	0.72
Baseline total score										
0	81	0.091 ± 0.149	40.0 ± 22.0	0	1.55 ± 4.24	1.46 ± 4.21	22.8	0.06 ± 0.147	< 0.001	0.41
≥ 1	743	23.0 ± 28.4	42.1 ± 23.0	0.62 ± 0.75	32.5 ± 34.5	9.53 ± 14.0	23.2	0.463 ± 0.679		0.68

SRM (standardized response mean) = Progression rate per month/SD of progression rate per month. † Analyses of covariance (ANCOVA). * $p < 0.05$, ** $p < 0.01$.

Table 3B. Erosion scores.

Comparisons	N	Baseline Score	Duration of RA, mo	Imputed Prestudy Progression Rate per Month	Last Visit Score	Change During Study	Months Elapsed	Progression Rate per Month During Study	p†	SRM
All with Paired Radiographs	824	10.9 ± 16.1	42 ± 23	0.307 ± 0.386	15.2 ± 16.7	4.3 ± 6.9	23.1	0.211 ± 0.355		0.59
Radiograph intervals (entry to final film)										
Completed study	276	10.1 ± 12.6	43 ± 23	0.290 ± 0.383	15.1 ± 16.4	4.9 ± 7.3	34.4	0.144 ± 0.216		0.67
25–35 mo	164	10.8 ± 12.4	39 ± 22	0.348 ± 0.428	16.1 ± 16.2	5.3 ± 7.4	27.6	0.203 ± 0.307		0.66
13–24 mo	218	12.4 ± 15.2	42 ± 22	0.307 ± 0.351	16.9 ± 18.8	4.5 ± 7.7	16.7	0.281 ± 0.483		0.58
6–12 mo	166	10.5 ± 13.3	43 ± 24	0.295 ± 0.394	12.5 ± 14.5	2.0 ± 3.1	8.4	0.239 ± 0.366	< 0.001	0.65
RA duration at entry										
12–24 mo	252	6.8 ± 7.9	16 ± 3.7	0.416 ± 0.490	11.2 ± 11.8	4.4 ± 6.7	23.5	0.212 ± 0.309	0.030	0.69
25–48 mo	254	10.1 ± 12.8	36 ± 7	0.296 ± 0.394	14.8 ± 17.3	4.7 ± 7.6	23.4	0.224 ± 0.403		0.56
49–84 mo	318	14.9 ± 16.1	67 ± 12	0.230 ± 0.254	18.8 ± 18.7	3.9 ± 6.4	22.6	0.200 ± 0.348		0.57
Ages										
> 60 yrs	231	14.2 ± 14.6	43.2 ± 23.6	0.388 ± 0.415	18.2 ± 17.8	4.0 ± 6.8	23.3	0.210 ± 0.396		0.53
40–60 yrs	487	10.4 ± 13.5**	42.5 ± 22.8	0.289 ± 0.375	14.7 ± 16.9	4.3 ± 7.0	23.1	0.212 ± 0.341		0.62
< 40 yrs	106	6.5 ± 8.3	36.3 ± 21.8	0.211 ± 0.338	11.1 ± 11.8	4.6 ± 6.4	22.9	0.211 ± 0.320	0.356	0.66
Sex										
Male	241	10.0 ± 12.4	39.4 ± 23.7	0.291 ± 0.371	14.3 ± 15.6	4.3 ± 7.0	23.9	0.194 ± 0.323	0.544	0.60
Female	583	11.3 ± 13.9	42.9 ± 22.6	0.314 ± 0.393	15.6 ± 17.1	4.3 ± 6.9	22.8	0.218 ± 0.367		0.59
Corticosteroid use										
No prednisone	627	10.2 ± 13.0**	41 ± 23	0.300 ± 0.399	14.3 ± 16.3	4.2 ± 6.8	23.3	0.206 ± 0.351		0.59
Prednisone	197	13.4 ± 14.6	43 ± 24	0.329 ± 0.345	18.1 ± 17.6	4.7 ± 7.3	22.5	0.228 ± 0.365	0.994	0.62
Prior DMARD										
No	630	8.9 ± 11.9**	38.1 ± 22.0	0.294 ± 0.403	13.1 ± 15.4	4.2 ± 6.9	23.6	0.207 ± 0.348		0.59
Yes	194	17.4 ± 16.0	53.9 ± 21.4	0.348 ± 0.324	21.9 ± 19.0	4.5 ± 7.0	21.5	0.226 ± 0.374	0.149	0.60
Rheumatoid factor										
Negative, ≤ 60 IU	272	6.8 ± 10.0	42.2 ± 24.2	0.212 ± 0.322	8.7 ± 12.8	1.9 ± 4.4	24.2	0.082 ± 0.193	< 0.001	0.42
Positive	552	13.0 ± 14.4**	41.7 ± 22.4	0.354 ± 0.406	18.4 ± 17.4	5.5 ± 7.5	22.4	0.275 ± 0.397		0.69
61–187	182	10.9 ± 12.6	42 ± 22	0.288 ± 0.305	14.9 ± 14.8	4.0 ± 6.1	23.7	0.190 ± 0.302		
188–640	183	13.4 ± 15.0	41 ± 23	0.366 ± 0.418	19.4 ± 18.3	6.1 ± 7.7	21.4	0.307 ± 0.409		
> 640	187	14.6 ± 15.4	42 ± 24	0.406 ± 0.470	20.9 ± 18.5	6.4 ± 8.6	22.0	0.325 ± 0.450		
ESR at baseline										
≤ 30	93	6.7 ± 9.6	40.5 ± 24.3	0.214 ± 0.317	10.1 ± 12.7	3.3 ± 6.2	22.4	0.150 ± 0.267	< 0.001	0.56
30–50	434	10.0 ± 12.4**	42.5 ± 22.9	0.269 ± 0.320	10.0 ± 12.4	3.8 ± 6.4	23.9	0.170 ± 0.279		0.61
> 50	295	13.6 ± 15.4	41.7 ± 22.6	0.388 ± 0.467	19.0 ± 18.7	5.4 ± 7.8	22.3	0.291 ± 0.453		0.64
CRP at baseline										
≤ 0.60 (negative)	212	6.2 ± 8.8	41.8 ± 23.4	0.201 ± 0.321	8.3 ± 10.8	2.1 ± 4.4	24.9	0.096 ± 0.229	< 0.001	0.42
0.61–1.34	211	8.3 ± 10.9**	41.5 ± 22.9	0.228 ± 0.280	11.5 ± 13.5	3.1 ± 5.3	23.2	0.136 ± 0.216		0.63
1.35–3.28	215	13.8 ± 15.5	41.7 ± 22.6	0.386 ± 0.448	19.0 ± 18.1	5.1 ± 7.2	22.5	0.267 ± 0.404		0.66
> 3.28	185	15.9 ± 15.5	42.3 ± 23.1	0.429 ± 0.429	23.1 ± 19.3	7.2 ± 9.2	21.7	0.366 ± 0.457		0.80
Painful joints, n										
0–21	266	8.8 ± 11.7	42.8 ± 23.8	0.242 ± 0.321	11.9 ± 13.6	3.1 ± 4.8	22.5	0.156 ± 0.245	0.036	0.64
22–33	281	10.5 ± 12.7**	41.4 ± 22.5	0.297 ± 0.361	14.7 ± 15.9	4.1 ± 6.8	23	0.214 ± 0.370		0.58
34–68	275	13.3 ± 15.4	41.6 ± 22.6	0.376 ± 0.448	19.0 ± 19.4	5.7 ± 8.4	23.9	0.262 ± 0.416		0.63
Swollen joints, n										
0–15	273	8.8 ± 12.3	42.0 ± 23.6	0.251 ± 0.356	11.9 ± 14.8	3.1 ± 5.0	23.1	0.149 ± 0.231	0.008	0.65
16–25	263	10.2 ± 12.7**	41.0 ± 22.6	0.303 ± 0.399	14.5 ± 15.9	4.3 ± 7.1	23.3	0.212 ± 0.381		0.56
26–66	286	13.6 ± 14.9	42.9 ± 22.7	0.359 ± 0.389	19.1 ± 18.4	5.5 ± 8.1	23	0.271 ± 0.413		0.66
20% composite responders										
Responders	536	10.3 ± 12.9	40.7 ± 22.9	0.305 ± 0.402	14.2 ± 16.2	4.0 ± 6.8	25.6	0.169 ± 0.303		0.56
Nonresponders	288	12.2 ± 14.3	44.2 ± 22.9	0.311 ± 0.356	17.1 ± 17.4	4.9 ± 7.2	18.5	0.290 ± 0.424	0.001	0.68
50% composite responders										
Responders	335	8.8 ± 11.6	40.7 ± 23.4	0.261 ± 0.367	11.7 ± 14.1	2.9 ± 5.3	27.2	0.112 ± 0.211		0.53
Nonresponders	489	12.4 ± 14.4	42.7 ± 22.7	0.338 ± 0.397	17.7 ± 17.9	5.3 ± 7.7	20.3	0.279 ± 0.412	0.001	0.68
Baseline erosion score										
0	81	0.09 ± 0.149	40.0 ± 22.0	0	0.69 ± 2.1	0.60 ± 2.15	22.8	0.03 ± 0.078	< 0.001	0.38
≥ 1	743	12.1 ± 13.7	42.1 ± 23.0	0.39 ± 0.393	16.8 ± 16.8	4.7 ± 7.14	23.2	0.23 ± 0.367		0.63

† Analyses of covariance (ANCOVA). ** p ≤ 0.01.

Table 3C. Joint space narrowing scores.

Comparisons	N	Baseline Score	Duration of RA, mo	Imputed Prestudy Progression Rate per Month	Last Visit Score	Change During Study	Months Elapsed	Progression Rate per Month During Study	p†	SRM
All with Paired Radiographs	824	9.8 ± 16.1	42 ± 23	0.253 ± 0.416	14.3 ± 19.3	4.4 ± 7.8	23.1	0.212 ± 0.376		0.56
Radiograph interval (entry to final film)										
36 mo	276	8.9 ± 15.6	43 ± 23	0.220 ± 0.373	14.6 ± 19.0	5.72 ± 9.19	34.4	0.168 ± 0.267		0.63
25–35 mo	164	9.5 ± 15.8	39 ± 22	0.296 ± 0.525	14.3 ± 19.6	4.8 ± 7.5	27.6	0.182 ± 0.281		0.65
13–24 mo	218	10.8 ± 17.0	42 ± 22	0.263 ± 0.427	15.1 ± 20.6	4.3 ± 7.8	16.7	0.265 ± 0.432		0.61
6–12 mo	166	10.4 ± 16.2	43 ± 24	0.252 ± 0.341	12.4 ± 17.7	2.1 ± 4.3	8.4	0.244 ± 0.505	0.033	0.48
RA duration at entry										
12–24 mo	252	4.7 ± 8.0	16 ± 3.7	0.298 ± 0.501	8.9 ± 12.0	4.2 ± 7.5	23.5	0.195 ± 0.329	0.733	0.59
25–48 mo	254	8.4 ± 15.0	36 ± 7	0.242 ± 0.443	13.0 ± 18.4	4.6 ± 8.1	23.4	0.209 ± 0.362		0.58
49–84 mo	318	15.0 ± 19.9	67 ± 12	0.227 ± 0.303	19.5 ± 23.1	4.5 ± 7.8	22.6	0.228 ± 0.421		0.54
Ages										
> 60 yrs	231	14.1 ± 19.1	43.2 ± 23.6	0.366 ± 0.529	17.9 ± 21.1	3.9 ± 6.1	23.3	0.195 ± 0.302		0.66
40–60 yrs	487	8.6 ± 15.2**	42.5 ± 22.8	0.210 ± 0.338	13.1 ± 18.8	4.5 ± 8.2	23.1	0.215 ± 0.407		0.53
< 40 yrs	106	6.3 ± 10.6	36.3 ± 21.8	0.205 ± 0.422	11.5 ± 15.9	5.3 ± 8.9	22.9	0.233 ± 0.379	0.101	0.61
Sex										
Male	241	7.8 ± 14.2	39.4 ± 23.7	0.203 ± 0.332	11.8 ± 16.8	4.1 ± 6.6	23.9	0.177 ± 0.281	0.231	0.63
Female	583	10.7 ± 16.8*	42.9 ± 22.6	0.274 ± 0.445	15.2 ± 20.2	4.6 ± 8.2	22.8	0.226 ± 0.409		0.55
Corticosteroid use										
No prednisone	627	8.7 ± 15.4**	41 ± 23	0.234 ± 0.432	13.0 ± 18.8	4.3 ± 8.1	23.3	0.205 ± 0.373		0.55
Prednisone	197	13.5 ± 17.7	43 ± 24	0.313 ± 0.356	18.3 ± 20.4	4.8 ± 6.8	22.5	0.233 ± 0.387	0.961	0.60
Prior DMARD										
No	630	7.4 ± 13.7**	38.1 ± 22.0	0.228 ± 0.426	11.6 ± 16.9	4.3 ± 7.6	23.6	0.200 ± 0.349		0.57
Yes	194	17.8 ± 20.3	53.9 ± 21.4	0.333 ± 0.375	22.7 ± 23.8	4.9 ± 8.3	21.5	0.250 ± 0.452	0.931	0.55
Rheumatoid factor										
Negative (≤ 60)	272	6.6 ± 12.2	42.2 ± 24.2	0.178 ± 0.347	8.6 ± 14.7	2.1 ± 6.0	24.4	0.084 ± 0.219	< 0.001	0.38
Positive	552	11.4 ± 17.5**	41.7 ± 22.4	0.290 ± 0.442	17.0 ± 20.7	5.6 ± 8.3	22.4	0.275 ± 0.419		0.66
61–187	182	10.3 ± 16.5	42 ± 22	0.253 ± 0.355	14.5 ± 18.4	4.2 ± 6.5	23.7	0.194 ± 0.302		
188–640	183	11.8 ± 17.6	41 ± 23	0.317 ± 0.498	18.1 ± 20.7	6.3 ± 8.4	21.4	0.313 ± 0.425		
> 640	187	12.1 ± 18.5	42 ± 24	0.301 ± 0.460	18.4 ± 22.5	6.3 ± 9.6	22	0.317 ± 0.496		
ESR at baseline										
≤ 30	93	5.4 ± 10.1	40.5 ± 24.3	0.161 ± 0.279	7.8 ± 12.2	2.4 ± 4.3	22.4	0.097 ± 0.158	0.001	0.61
31–50	434	8.7 ± 14.7**	42.5 ± 22.9	0.216 ± 0.337	12.8 ± 18.1	4.2 ± 7.7	23.9	0.187 ± 0.344		0.54
≥ 50	295	12.9 ± 19.0	41.7 ± 22.6	0.337 ± 0.530	18.4 ± 22.0	5.5 ± 8.7	22.3	0.282 ± 0.450		0.63
CRP at baseline										
≤ 0.60 (negative)	212	6.2 ± 13.5	41.8 ± 23.4	0.183 ± 0.401	8.1 ± 15.1	2.0 ± 5.1	24.9	0.087 ± 0.211	< 0.001	0.41
0.61–1.34	211	7.3 ± 12.9**	41.5 ± 22.9	0.179 ± 0.284	10.6 ± 15.7	3.3 ± 6.4	23.2	0.148 ± 0.277		0.53
1.35–3.28	215	11.7 ± 17.2	41.7 ± 22.6	0.298 ± 0.464	17.0 ± 19.8	5.2 ± 7.2	22.5	0.252 ± 0.358		0.70
> 3.28	185	14.7 ± 19.3	42.3 ± 23.1	0.367 ± 0.469	22.4 ± 23.1	7.6 ± 10.8	21.7	0.383 ± 0.540		0.71
Painful joints, n										
0–21	266	8.1 ± 15.7	42.8 ± 23.8	0.202 ± 0.397	11.5 ± 17.6	3.4 ± 5.4	22.5	0.172 ± 0.334	0.088	0.51
22–33	281	9.9 ± 15.4	41.5 ± 22.5	0.249 ± 0.362	14.1 ± 18.2	4.3 ± 7.2	23	0.203 ± 0.329		0.62
34–68	275	11.4 ± 17.1	41.6 ± 22.6	0.306 ± 0.478	17.1 ± 21.6	5.7 ± 9.9	23.9	0.257 ± 0.449		0.57
Swollen joints, n										
0–15	273	8.5 ± 15.4	42.0 ± 23.6	0.231 ± 0.448	11.7 ± 18.0	3.2 ± 6.0	23.1	0.150 ± 0.258	0.005	0.58
16–25	263	8.4 ± 14.0**	41.0 ± 22.6	0.220 ± 0.355	12.8 ± 16.6	4.4 ± 6.9	23.3	0..208 ± 0.371		0.56
26–66	286	12.5 ± 18.3	42.9 ± 22.7	0.305 ± 0.434	18.1 ± 22.1	5.6 ± 9.7	23	0.272 ± 0.458		0.59
20% Composite responses										
Responders	536	8.9 ± 15.1	40.7 ± 22.9	0.171 ± 0.320	13.0 ± 18.1	4.1 ± 7.7	25.6	0.236 ± 0.413		0.57
Nonresponders	288	11.6 ± 17.8*	44.2 ± 22.9	0.285 ± 0.421	16.6 ± 21.1	5.0 ± 7.9	18.5	0.288 ± 0.454	< 0.001	0.63
50% composite responses										
Responders	335	7.4 ± 13.6	40.7 ± 23.4	0.195 ± 0.367	10.6 ± 15.9	3.3 ± 6.6	27.2	0.125 ± 0.244		0.51
Nonresponders	489	11.5 ± 17.5**	42.7 ± 22.7	0.293 ± 0.443	16.7 ± 21.0	5.2 ± 8.4	20.3	0.271 ± 0.435	< 0.001	0.63
Baseline narrowing score										
0	81	0	40 ± 22.0	0	0.77 ± 2.8	0.77 ± 2.8	22.8	0.029 ± 0.095	< 0.001	0.30
≥ 1	743	10.9 ± 16.6	42.1 ± 23.0	0.232 ± 0.390	15.7 ± 19.8	4.8 ± 8.1	23.2	0.232 ± 0.390		0.59

† Analyses of covariance (ANCOVA). * $p < 0.05$, ** $p < 0.01$.

The secondary analyses of radiographic progression are presented in Table 4. Overall, 43% of the paired radiographs had no increase in erosion score, and 59% had no new erosions in previously non-eroded joints. The subanalyses shown in Table 4 show significant associations with time in study, with baseline RF positivity, ESR, and absence of erosions, and with 20% and 50% composite clinical responses for each of the secondary analyses. Painful and swollen joint counts at entry were not associated with the enumeration of patients with no increase in erosions or with no newly eroded joints (Table 4).

SRM for progression rates per month during the study are shown in Table 3. Larger SRM sizes indicate more rapid progression of radiographic damage. Table 5 shows SRM for radiographic progression of non-DMARD-treated patient groups during some prospective randomized clinical trials.

DISCUSSION

One might be concerned that, because of selection bias, patients who entered the longterm etodolac trial may have had mild and nonprogressive RA that had not required

Table 4. Secondary analyses of radiographic progression.

	Erosion Score No. (%) with No Increase Erosion Score	p†	Newly Eroded Joints No. (%) with No Newly Eroded Joints	p†
All with Paired Radiographs	356 (43)		483 (59)	
Radiograph interval (entry to final film)				
Completers	121 (44)		161 (58)	
25–35 mo	86 (52)		106 (65)	
13–24 mo	100 (46)		133 (61)	
6–12 mo	49 (30)	0.001	83 (50)	0.045
RA duration at entry				
12–24 mo	106 (42)	0.908	142 (56)	0.574
25–48 mo	111 (44)		148 (58)	
49–84 mo	139 (44)		193 (61)	
Age, yrs				
> 60	97 (42)		144 (62)	
40–60	204 (42)		273 (56)	
< 40	55 (52)	0.154	66 (62)	0.200
Sex				
Male	104 (43)	0.985	140 (58)	0.844
Female	252 (43)		343 (59)	
Corticosteroid use				
No prednisone	273 (44)	0.728	370 (59)	0.682
Prednisone	83 (42)		113 (57)	
Prior DMARD				
No	281 (45)		364 (58)	
Yes	75 (39)	0.144	119 (61)	0.378
Rheumatoid factor				
Negative, ≤ 60	167 (61)	0.001	198 (73)	0.001
Positive	189 (34)		285 (52)	
ESR at baseline				
≤ 30	53 (57)	0.001	65 (70)	0.001
31–50	200 (46)		263 (61)	
≥ 51	103 (35)		155 (53)	
Painful joints, n				
0–21	120 (45)	0.659	162 (61)	0.674
22–33	116 (41)		161 (57)	
34–68	120 (44)		160 (58)	
Swollen joints, n				
0–15	130 (48)	0.153	173 (63)	0.056
16–25	113 (43)		157 (60)	
26–66	113 (40)		153 (53)	
20% composite responders	255 (48)	< 0.001	341 (64)	< 0.001
50% composite responders	172 (51)	< 0.001	228 (68)	< 0.001
Erosions at baseline				
0	67 (83)	0.001	67 (83)	0.001
≥ 1	289 (39)		416 (56)	

† Analyses of covariance (ANCOVA).

Table 5. Radiographic progression of non-DMARD-treated patients during some prospective randomized clinical trials.

Report	RA Duration, mean yrs	RF+, %	Number Analyzed (number entered)	Study Duration	Scoring Method	Entry Score, mean	SRM				SRM of Comparison DMARD
							Total Score	Erosions	Joint Space Narrowing	Other Method	
Sharp[4]											
(a) Leflunomide vs MTX vs placebo	6.9	60	83 (118)[1]	12 mo	Sharp	(a) 25.4 (total)	0.55 (2.16/3.95)	0.46 (0.84/1.82)	0.46 (1.24/2.70)		(a) Lef 0.12 MTX 0.27 } Total score
(b) Leflunomide vs SSZ vs placebo	5.7	83	62 (91)	6 mo	Sharp	(b) 46.2 (total)	0.59 (5.88/10.0)	0.51 (2.07/4.09)	0.51 (3.81/7.45)		(b) SSZ 0.23 Lef 0.08 } Total score
Smolen[2]											
Leflunomide vs SSZ vs placebo	5.7	83	60 (91)	6 mo	Larsen[24] (per joint)	1.49 per joint	—	0.55 (0.05/0.09)	—		Lef 0.33 SSZ 0.33
Bluhm[22]											
Minocycline vs placebo	8.8	57	96 (110)[2]	12 mo	Sharp (per month)	7.5 (erosions) JSN 16.1	—	0.32 (0.12/0.37)	0.41 (0.20/0.48)		Minocycline Erosion = 0.15 JSN = 0.36
Bresnihan[5]											
IL-1 ra vs placebo	3.7	69	83 (119)	6 mo	(a) Larsen (b) Number of eroded joints	(a) 15.4 (b) 5.0	—	(a) 0.63 (6.4/10.11)	—	(b) 0.66 (2.6/3.92)	(a) IL ra (Larsen) 30 mg/day = 0.48 75 mg/day = 0.37 150 mg/day = 0.46
Hannonen[20]											
SSZ vs placebo	0.5	67	37 (40)	12 mo (70% on gold by 24 wks)	Sharp	1.9 (total)	0.69 (7.1/10.33)	0.78 (4.4/5.66)	0.58 (2.7/4.66)		SSZ Total = 0.66 Erosion = 0.75 JSN = 0.50
Førre[21]											
Cyclosporine vs placebo	8.1	?	23 (61)	12 mo (prednisolone 15 mg/day tapered to 5.3 mg/day	(a) Larsen (b) Number of erosions	(a) 1.43 per jt (b) 4.14	—	(a) 0.71 (0.17/0.24)	—	(b) 0.61 (1.03/1.68)	Cyclosporine (a) Larsen = 0.04 (b) No. of erosions = 0.04
Pooled etodalac vs Ibuprofen (current report)	3.5	67	824 (1433)	36 mo	Modified Sharp and Genant (per mo)	20.7 (total) 10.9 (erosions) 9.8 (JSN)	0.64 (0.423/0.658)	0.59 (0.211/0.355)	0.56 (0.212/0.376)	—	NA

[1] Intent-to-treat (ITT) analysis of 83 patients with paired radiographs. Only 31 completed 48 weeks of placebo treatment. 35 added a DMARD about 27 weeks before the final radiograph. 17 had the final radiograph at early departure from the study. [2] ITT analysis of 96 patients with paired radiographs. However, only 80 of the 110 completed 12 months of placebo treatment. SRM (standardized response mean) = mean change during study/SD of change. MTX: methotrexate, SSZ: sulfasaline, Lef: leflunomide, NA: not applicable.

DMARD for at least 6 months. Today we cannot understand why patients with active RA would want to enter a 3-year study comparing 2 NSAID. However, patients entering the etodolac trial 19 years ago had fewer well-tolerated DMARD options, and the study hypothesis (based on a prior open study) was that etodolac would retard radiographic progression. Consequently, the patients entering the etodolac study had active RA with 29 tender joints, 22 swollen joints, ESR 49, RF 578 IU, and 69% RF positive, similar to that of patients entering today's DMARD and biological agent trials. For example, in the etanercept versus MTX early RA trial[7], mean tender joint count was 30 ± 16, swollen joint count 24 ± 12; the infliximab/MTX versus MTX study[8] had 31 ± 18 tender joints, 21 ± 12 swollen joints, and ESR 49.

The longterm etodolac study and the placebo-control groups from selected published clinical trials (Tables 2 and 5) illustrate the progression of joint radiographic damage by non-DMARD-treated groups in moderate to longterm prospective controlled clinical trials. Although a substantial proportion of entering patients (with intolerable disease activity and presumably more rapid radiographic progression) drop out before 6 months, radiographic progression of the remaining patients has been sufficient to detect the

benefit of an effective treatment[2-5], and to identify patient characteristics associated with progression.

Concomitant drugs received by the patients during the longterm etodolac study were similar to those received by more recent placebo-group patients. Almost all patients in the cited studies also received NSAID, and low dose prednisone was allowed. Twenty-three percent of the etodolac study patients continued low dose prednisone, compared to 56% and 45% of the placebo patients in the 2 leflunomide studies[2,4], 40% in the IL-1ra study[5], 100% in the cyclosporine study[21], and 7.5% in the sulfasalazine study[20].

Withdrawals and missing radiographs are frequent in study groups that are not permitted to use DMARD (Table 2). Patient withdrawal was frequent during this 3-year study, but the proportions remaining after 24 (57.5%) and 48 weeks (46%) were similar to those in the placebo arms of studies of leflunomide[2,4], sulfasalazine[20], cyclosporine[21], or IL-1ra[5]. After 98 and 147 weeks, 31% and 19%, respectively, of our patients remained evaluable. These proportions appear to be representative of the retention rates when patients with active RA are randomized to prolonged non-DMARD treatment. Some clinical trials increase the number of placebo patients available for intent-to-treat radiographic analysis by obtaining the protocol-specified final radiographs at the nominal end of the trial even in patients who withdrew and started a DMARD during the trial, assuming that delayed onset of radiographic benefit from the newly started DMARD will permit sufficient carryover progression to maintain the integrity of the placebo effect long enough for a valid analysis. For example, 70% of the placebo patients in the sulfasalazine study by Hannonen, *et al*[20] had started gold by the 24th week, but the radiographic analysis was done at 48 weeks. Similarly, in the 48-week leflunomide/MTX[4] trial only 31 of the 118 patients randomized to placebo completed 48 weeks of placebo treatment, but 83 were included as placebo-treated in the intent-to-treat analysis. To the uncertain extent that radiographic progression was affected by the added DMARD or other treatments permitted by the study after withdrawal, the "placebo" group data is compromised, and may underestimate the progression on placebo alone.

In the longterm etodolac study, no DMARD was permitted for 6 months before study entry, and progression rates are calculated only for the time intervals that the patients remained on study. One might anticipate that patients who dropped out before the radiograph scheduled for 6 months had more rapid radiographic progression than those with paired radiographs. This assumption is supported by higher 20% (65% vs 50% responders) and 50% (41% vs 28% responders) composite clinical responses[17] in the 824 patients with paired radiographs, all of whom remained in the study for at least 6 months compared to all 1433 patients. When we compared disease activity measures of 284 completers with the 557 who dropped out for lack of efficacy, entry joint counts were not different, but baseline patient and physician global assessments, ESR, CRP, and RF values were significantly less severe in the completers. At final visit, all of these measures were much less severe in the completers[25]. Therefore, the progression rates that we report here, as well as those of the placebo-control groups in the published studies, almost certainly underestimate the true progression rates in the entire non-DMARD-treated study population (Table 3).

It has been suggested that radiographic damage progresses more rapidly in the first several years of RA, with slower progression subsequently[26]. A ceiling effect due to scoring methods has been hypothesized[27], but may be important only in advanced disease. Several patterns of progression have been noted in prospective observational studies[28,29], but the effect of ad lib DMARD treatment is not clear. In our patients who did not receive DMARD during the study, erosion progression rates were marginally different ($p = 0.03$), but the total and JSN radiographic progression rates during an average of 23 months' followup were not significantly different in the cohorts with 12–24 months, 25–48 months, and 49–84 months of RA duration at study entry, suggesting a relatively linear progression for the study population, and agreeing with the findings of Wolfe and Sharp[30] and Hulsmans, *et al*[31].

Age at study entry and sex were not significantly associated with monthly progression rates. The progression rates of the 194 patients with a history of prior DMARD use (6 or more months before study entry) were not significantly different than those of the 630 patients who had never been treated with a DMARD. At entry, higher average radiographic damage scores of 197 patients currently using prednisone (mean dose 4.41 mg/day) suggested greater prior disease activity, but their progression rates during the study were not smaller than the rates of the 627 patients who did not take corticosteroids[32]; these data are not consistent with studies suggesting that low dose corticosteroids prevent erosions in RA[33,34].

The presence of RF was strongly associated with radiographic progression[35], which appeared to plateau at a higher rate in patients with RF > 187 IU. Progression was much less rapid in seronegative patients. Higher ESR and CRP values[36] and higher baseline swollen joint counts were significant predictors of more rapid progression of radiographic damage. Painful joint counts at baseline were marginally associated with progression of erosion scores ($p = 0.036$) and JSN scores ($p = 0.088$), but not with changes in total scores ($p = 0.34$). Patients with better clinical responses as measured by 20% and 50% composite criteria[17] had slower progression of radiographic damage. Because assays for the genetic rheumatoid epitope were not available in this study population, we cannot comment on their reported association with radiographic damage[37].

Analyses of the numbers of patients with no increase in

erosion scores, and with no newly eroded joints (Table 4), generally support the findings of the primary analyses of radiographic scores (Table 3), and appear to add only descriptive information. We cannot comment on radiographic progression in the joints of the forefoot because radiographs of the feet were not included in this study.

Because the radiographic damage scales used in published studies vary from paper to paper, even though the same process is being measured, we have calculated SRM sizes, which are unitless and may permit cross-study comparisons (see Materials and Methods). SRM differ slightly from effect sizes, but the use of SRM to compare trial results is not well established and must be interpreted cautiously. Using mean progression rate per month and its standard deviation, the SRM sizes for all patients with paired radiographs were 0.64 for total score, 0.59 for erosion score, and 0.56 for JSN score. These are negative SRM sizes, since the joint damage is getting progressively worse, and are classified as "medium" by Cohen[18]. SRM sizes were "small" for the subgroups with negative RF and for those with no erosions at baseline, but were "medium" for the other comparison subgroups. SRM sizes also were "medium" for the non-DMARD-treated placebo groups in most of the published trials shown in Table 5, but were "small" for the placebo group in the minocycline study[22], which included more seronegative patients, and for the placebo group from the leflunomide/MTX/placebo[4] study, which permitted a rescue DMARD before the final radiographs were done. Surprisingly, most SRM sizes in Table 5 were "medium," even though scoring methods (Sharp[12], Larsen[24], number of eroded joints, number of erosions), average disease durations at entry (0.5 to 8.1 yrs), study duration (6 mo to 3 yrs), mean change in radiographic score during study, and study sites varied widely between studies. When the mean change was larger, its SD tended to be larger, resulting in SRM sizes that were similar to those seen when mean change and SD were smaller. In those studies that reported significant treatment-associated radiographic benefit, the SRM sizes of the comparison DMARD generally were substantially smaller than those of their placebo-control groups (Table 5).

Our findings in non-DMARD-treated patients generally confirm previous reports based on observational studies that did not restrict DMARD use. In an observational study of 256 patients with early RA who were followed between 1973 and 1993 for a mean of 8.6 years, 78.5% of whom were treated with DMARD, Wolfe and Sharp[30] noted mean annual progression rates (Sharp scores) of paired hand/wrist radiographs of 4.5 units/yr for total, 1.9 for erosions, and 2.6 for JSN scores. In a prospective study of 502 patients with early RA who were randomized to hydroxychloroquine, aurothioglucose, or MTX treatment and followed for up to 6 years (mean 2.7 yrs), the rates of progression in hand/wrist radiographs were: total score 5.1, erosion score 2.9, JSN score 2.2 Sharp units per year[31]. In the absence of DMARD treatment, our patients had similar mean annual progression rates of 5.08 (total), 2.5 (erosions), and 2.5 (JSN) units per year during an average followup of 23 months. This implies minimal benefit from the ad lib use of DMARD, and indeed Wolfe and Sharp were unable to demonstrate radiographic benefit from the DMARD used during their observational study; however, selection bias in the observational studies and dropout bias in the clinical trials may confound the results. After an average of 16.2 years duration of RA, Abu-Shakra, *et al*[38] reported Sharp scores of hand/wrist radiographs of 22 Russian Jewish patients who were never treated with DMARD. Imputed annual progression rates from disease onset were 5.7 (total), 2.6 (erosions), and 3.1 (JSN) units per year, similar to the annualized rates that we observed over 23 months.

In conclusion, the progression rate of RA radiographic damage in non-DMARD-treated patients appears to be rapid enough so that clinically important retardation of joint damage should be detectable in reasonable-sized placebo-controlled studies of 6 to 12 months duration. The patient retention and radiographic progression rates presented here may be useful as historical background data in the planning and evaluation of longterm clinical trials that evaluate joint radiographic outcomes.

APPENDIX

The following Long-term Etodolac Study Investigators participated and provided the patients and data that were analyzed for this report. John L. Abruzzo, MD; R. Franklin Adams, MD; Raymond A. Adelizzi, DO; Steven P. Akre, MD; Daniel J. Appelrouth, MD; Paul A. April, MD; Mitchell C. Austin, MD; Anne M. Bacon, MD; David F. Bjarnason, MD; Gilbert B. Bluhm, MD; Barry I. Bockow, MD; Anthony Bohan, MD; Walter Bonner, MD; Jeffrey E. Booth, MD; Patrick Box, MD; Norman M. Bress, MD; Alan Brodsky, MD; Jacques R. Caldwell, MD; Beverly A. Carpenter, MD; R. Deaver Collins, MD; Ronald I. Collins, MD; John S. Davis, MD; Matthew W. Duncan, MD; William M. Edwards, MD; James A. Engelbrecht, MD; Stephen J. Farber, MD; Justus J. Fiechtner, MD; Roy M. Fleischmann, MD; Frederick J.A. Font, MD; Bernard F. Germain, MD; Kenneth P. Glassman, MD; Alan P. Goldman, MD; Alben G. Goldstein, MD; Gary V. Gordon, MD; Richard S. Gordon, MD; Jose L. Granda, MD; Frank M. Graziano, MD; Robert A. Greenwald, MD; William B. Gruhn, MD; Joseph S. Habros, MD; E.R. Harris, MD; Gerald S. Harris, MD; James K. Hensarling, MD; Thomas J. Hirsch, MD; Cameron B. Jones, MD; Stanley B. Kaplan, MD; Michael I. Keller, MD; Norman N. Kohn, MD; A. Lewis Kolodny, MD; William L. Lages, MD; Bob G. Lanier, MD; Jeffrey G. Lawson, MD; Donald G. Leonard, MD; Michael R. Liebling, MD; Herbert B. Lindsley, MD; John A. Lipani, MD; Richard Lipson, MD; Charles L. Ludivico, MD; Christopher J. Lynch, MD; Alan H. Mallace, MD; Joseph A. Markenson, MD; Lawrence P. McAdam, MD; E. Chester McDanald, MD; Jeffrey Miller, MD; Kenneth A. Miller, MD; John A. Mills, MD; Bernard J. Mullen, MD; David H. Neustadt, MD; Michael A. O'Hanlan, MD; Richard S. Panush, MD; William B. Pincus, MD; Jeffrey E. Poiley, MD; William Powell, MD; Daniel S. Prince, MD; Ronald J. Rapoport, MD; William A. Riley, MD; Robert A. Roschmann, MD; Sanford H. Roth, MD; Gary Ruoff, MD; Joel E. Rutstein, MD; Robert T. Salzman, MD; Jerome J. Schnapp, MD; Abdollah Shams-Pirzadeh, MD; Stephen R. Shaul, MD; Murray C. Sokoloff, MD; Sheldon D. Solomon, MD; George T. Spencer-Green, MD; Roland R. Springgate, MD; William T. Tatum, MD; Robert G. Trapp, MD; Robert A. Turner, MD; Thomas V. Valentine, MD; Arthur M. Virshup, MD;

Ronald I. Weitzner, MD; James H. Wild, MD; Frederick Wolfe, MD; Muhammad B. Yunus, MD.

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