

Relative Sensitivity to Change of the Erythrocyte Sedimentation Rate and Serum C-Reactive Protein Concentration in Rheumatoid Arthritis

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ABSTRACT. Objective. To compare the sensitivity to change of the erythrocyte sedimentation rate (ESR) and serum C-reactive protein (CRP) concentration used as measures of rheumatoid arthritis (RA) activity.

Methods. A literature search was conducted to identify all clinical trials and observational studies of disease-modifying medications and corticosteroids in RA that reported results for both ESR and CRP before treatment and 4 weeks to 24 weeks after treatment in the same patients. For each test, effect sizes were computed as the change in the test with treatment divided by the pretreatment standard deviation. A pooled analysis was performed on the paired differences in effect sizes for ESR and CRP within each study.

Results. One hundred twenty-three studies with 184 active treatment arms were identified that included measurements of both ESR and CRP. Sixty-three studies with 90 active treatment arms provided sufficient data to permit calculation of effect sizes, and were included in the analysis. In the 36 treatment arms that reported results at 12 weeks, the ESR was more sensitive to change than the CRP, with a paired difference in effect sizes of 0.09 units (95% confidence interval 0.03, 0.15; $p = 0.005$). In the 76 treatment arms that reported results at 24 weeks, the ESR was also more sensitive to change than the CRP, with a paired difference in effect sizes of 0.11 units (95% CI 0.05, 0.17; $p = 0.0004$).

Conclusion. In these studies of disease-modifying medications in RA, the ESR was more sensitive to change than the CRP at 12 weeks and 24 weeks of treatment. Few studies examined changes in these measures at times earlier than 12 weeks. (J Rheumatol 2003;31:884-95)

Key Indexing Terms:

RHEUMATOID ARTHRITIS
C-REACTIVE PROTEIN

ERYTHROCYTE SEDIMENTATION RATE
SENSITIVITY TO CHANGE

The erythrocyte sedimentation rate (ESR) and the serum C-reactive protein (CRP) concentration are the 2 laboratory tests most commonly used in the evaluation of the activity of rheumatoid arthritis (RA)¹. Both tests have been judged acceptable measures of the acute phase response in the recommended core sets of endpoint measures for clinical trials in RA²⁻⁴. One reason for the lack of strong preference for either test may be that few comparisons of their evaluative properties have been done. In particular, little is known about the relative sensitivity to change of the ESR and CRP in RA. Sensitivity to change, or responsiveness, is the property that assesses how well a test captures changes in clinical status when they occur⁵. Tests that are sensitive to change will register large changes when a patient's clinical status improves, while insensitive measures remain rela-

tively stable despite noticeable clinical improvement. Tests that are more sensitive to change are preferred as endpoints in clinical trials because these tests are better able to capture changes with treatment when they occur. If either the ESR or CRP was shown to be more sensitive to change, the more sensitive test might become the preferred measure of the acute phase response in clinical trials in RA. This pooled analysis was performed to compare the relative sensitivity to change of the ESR and CRP in RA.

MATERIALS AND METHODS

Literature search. The search sought to identify all clinical trials and observational studies that measured both ESR and CRP in the same patients at the start of treatment with either a disease-modifying medication or corticosteroids, and after 4 weeks to 24 weeks of treatment. Medline was searched from 1966 through December 2002, using "rheumatoid arthritis" as the major subject heading and either "erythrocyte sedimentation rate" or "C reactive protein" as text words. Individual drug names ("prednisone," "methylprednisolone," "corticosteroids," "glucocorticoids," "hydroxychloroquine," "chloroquine," "aurothioglucose," "gold sodium thiomalate," "auranofin," "azathioprine," "sulfasalazine," "minocycline," "penicillamine," "methotrexate," "cyclosporine," "leflunomide," "infliximab," "etanercept," "anakinra," and "interleukin-1 receptor antagonist") were also searched as text words. In addition, the Cochrane Database was searched for trials of these medications in RA, and reference lists of retrieved articles were searched for additional studies.

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To be included, the study must have (1) studied adults with RA; (2) measured both the ESR and CRP in the same patients at the same time points; (3) provided means and standard deviations (or standard errors) for both tests before the start of treatment with a new disease-modifying medication or corticosteroid; (4) provided mean responses for both tests at some time between 4 weeks and 24 weeks after the start of treatment; (5) used quantitative methods, rather than semiquantitative methods such as tube dilutions, to measure CRP; and (6) have been published in English. Studies of single medications, combinations of medications (in which 2 or more medications were started at the same time), or staged approaches to treatment were included. The few studies that reported combined results of patients treated with different medications (here termed "mixtures") were also included. Studies of intravenous corticosteroids, which typically measured responses after several days, were excluded. Studies in which patients with RA were combined with patients with other diagnoses and could not be identified separately were also excluded. For studies published since 1994, authors and sponsoring pharmaceutical companies were contacted to obtain missing data, or to obtain data on the ESR and CRP expressed as means and standard deviations if the publication only reported median values. Because the retrieval of information for these studies was low, missing data were not sought for earlier studies.

For each study, information was abstracted on the study design (clinical trial versus observational study), number of subjects, medication, dose, methods used to measure the ESR and CRP, and ESR and CRP values at study entry and at every reported time between 4 weeks and 24 weeks after the start of treatment. Characteristics of each active treatment group, including mean or median patient age, mean or median duration of RA, and proportion of seropositive patients were also recorded. Each active treatment arm was considered separately.

Statistical analysis. The effect size was used as the measure of sensitivity to change. For each treatment arm of each study, the effect size of the ESR and CRP was computed as: (baseline value – followup value)/baseline standard deviation⁶. Positive effect sizes indicate that the ESR or CRP decreased with treatment, negative effect sizes indicate that the ESR or CRP increased with treatment, and effect sizes of zero indicate that the treatment had no effect on the ESR or CRP. Pooled estimates of the effect size for the ESR and CRP were estimated at each time point from 4 weeks to 24 weeks of treatment using random effects models^{7,8}. Pooled estimates of the effect sizes were weighted by the number of subjects in the treatment arm, so that larger studies, which presumably provide more accurate estimates of treatment effects, had a greater influence on the pooled effect size.

Each active treatment arm yielded a pair of effect sizes, one for the ESR and one for the CRP, based on the response of these tests to the same treatment in the same sample of patients. To compare the sensitivity to change of the ESR and CRP, the effect size of the CRP was subtracted from the paired effect size of the ESR to yield an effect size difference. Effect size differences were pooled among treatment arms using a fixed effects model to provide summary estimates of the relative sensitivity of the ESR and CRP. A positive paired effect size difference indicated that the ESR was more sensitive to change than the CRP, while a negative paired effect size difference indicated that the CRP was more sensitive to change than the ESR. Paired effect size differences were pooled separately for results reported at 4, 8, 12, 16, and 24 weeks. Paired effect size differences were also weighted by the number of subjects in the treatment arm, so that larger studies had a greater influence. Ninety-five percent confidence intervals (CI) of the paired effect size difference that excluded zero indicated a significant difference (at a Type I error rate of 0.05) in the effect size of the ESR and CRP.

RESULTS

Literature search. The literature search identified 123 studies with 184 active treatment arms of disease-modifying medications or corticosteroids that reported obtaining measurements of both ESR and CRP before treatment and

within the first 24 weeks of treatment. Sixty studies with 94 active treatment arms were excluded because only median values were reported (17 studies), followup data were not reported (15 studies), either the ESR or CRP data were not reported (12 studies), baseline means or standard deviations were not reported (12 studies), or the CRP was not measured quantitatively (4 studies). Missing data were solicited for 12 of these studies, but were not available. The most common medications in the excluded studies were sulfasalazine (13 treatment arms), intramuscular gold (12), cyclosporine (11), methotrexate (10), auranofin (11), and D-penicillamine (10 treatment arms). The median number of patients in the excluded treatment arms was 26; 68% of excluded treatment arms had fewer than 50 patients.

Sixty-three studies with 90 active treatment arms provided sufficient data to permit calculation of effect sizes for both the ESR and CRP, and were included in the analysis⁹⁻⁷¹. Additional data were provided by the authors or sponsors of 16 studies, which allowed these studies to be included. The most common medications in these treatment arms were methotrexate, cyclosporine, sulfasalazine, and combination therapies (Table 1). Sixty-two percent of the treatment arms were from clinical trials, and 38% from observational studies. The number of patients in the treatment arms ranged from 8 to 501, with a median of 42 patients. Sixty-six percent of treatment arms were from studies published in 1995 or later, and 31% of treatment arms included patients with a mean or median duration of RA of 2 years or less. Nine treatment arms reported results at 4 weeks, 7 at 8 weeks, 36 at 12 weeks, 11 at 16 weeks, and 76 treatment arms reported results at 24 weeks. Only one study reported results at 20 weeks, and this time point was therefore not examined.

Effect size difference at 4 weeks. Among 8 treatment arms (with 301 patients) that reported results at 4 weeks, the pooled effect size of the ESR was 0.29 and the pooled effect size of the CRP was 0.39 (Table 2). One study of oral prednisolone reported very large effect sizes for the ESR and CRP (1.07 for both), and was excluded as an outlier. In 6 of the 8 treatment arms, the effect size of the CRP was larger than that of the ESR. In the pooled analysis, the weighted paired effect size difference was -0.05, indicating that the CRP was slightly more sensitive to change than the ESR in these treatment arms, although not significantly so (Table 2).

Effect size difference at 8 weeks. Among the 7 treatment arms (with 177 patients) that reported results at 8 weeks, the pooled effect size of the ESR was 0.41 and the pooled effect size of the CRP was 0.45 (Table 2). In 5 of the 7 treatment arms, the effect size of the ESR was larger than that of the CRP. However, in the pooled analysis, the weighted paired effect size difference was -0.06, indicating a nonsignificant trend for the CRP to be more sensitive to change than the ESR. This result was largely due to one study of cyclosporine that demonstrated an effect size for CRP of

Table 1. Characteristics of studies and effect size for the ESR and CRP concentration, by medication*. Doses indicate starting or average doses.

Study	N	Design	Dose, mg/wk	Mean Age, yrs	Duration of RA, yrs	Proportion RF Positive	Mean ESR, mm/h	Mean CRP, mg/l		
Methotrexate										
Boerbooms, 1988 ⁹	14	Obs	7.5	59.0	16.0	88	65.6	45.9		
Drosos, 1990 ¹⁰	137	Obs	10	56.0	8.7	75	57.9	35.1		
Jeurissen, 1991 ¹¹	31	Trial	7.5	57.3	12.8	94	57.5	39.0		
Wiktorowicz, 1992 ¹²	34	Obs	7.5	48.8	10.3	88	71.4	43.6		
Lacki, 1994 ¹³	48	Obs	7.5	51.2	11.3	85	71.0	41.0		
Wascher, 1994 ¹⁴	8	Obs	15	58.0	NR	100	53.2	46.0		
Rau, 1997 ¹⁵	87	Trial	15	54.2	2.2	68	41.5	41.0		
El Miedany, 1998 ¹⁶	42	Obs	10	35.4	1.0	NR	59.0	111.4		
Rau, 1998 ¹⁷	58	Obs	15	59.0	9.6	80	55.1	43.8		
Rau, 1998 ¹⁷	93	Obs	15	57.2	7.7	88	56.7	50.8		
Rau, 1998 ¹⁷	38	Obs	15	55.5	8.3	82	59.3	47.3		
Strand, 1999 ¹⁸	182	Trial	7.5	53.3	6.5	59	33.8	18.8		
Emery, 2000 ¹⁹	498	Trial	10	57.8	3.8	NR	51.6	40.7		
Ribbens, 2000 ²⁰	9	Trial	7.5	NR	NR	NR	42.0	53.0		
Lerndal, 2000 ²¹	50	Trial	10	57.1	0.7	31	49.9	53.9		
Bathon, 2000 ²²	217	Trial	20	49.0	1.0	89	39.7	37.0		
Hamilton, 2001 ²³	69	Trial	10	60.0	6.0	62	46.4	47.1		
Effect Size										
			Week 4	Week 8	Week 12	Week 16	Week 24			
			ESR	CRP	ESR	CRP	ESR	CRP		
Methotrexate										
Boerbooms, 1988 ⁹			—	0.92	0.81	—	—	1.03	1.23	
Drosos, 1990 ¹⁰			—	—	0.50	0.05	—	—	0.65	0.22
Jeurissen, 1991 ¹¹			—	—	—	—	—	—	0.90	0.86
Wiktorowicz, 1992 ¹²			—	—	0.83	0.99	—	—	1.29	1.00
Lacki, 1994 ¹³			—	—	1.11	0.92	—	—	1.25	0.96
Wascher, 1994 ¹⁴			—	—	—	—	1.39	0.84	—	—
Rau, 1998 ¹⁶			—	—	0.51	0.58	—	—	0.76	0.53
El Miedany, 1998 ¹⁶			—	—	0.68	0.77	—	—	—	—
Rau, 1998 ¹⁷			—	—	—	—	—	—	0.98	0.64
Rau, 1998 ¹⁷			—	—	—	—	—	—	0.62	0.85
Rau, 1998 ¹⁷			—	—	—	—	—	—	0.52	0.50
Strand, 1999 ¹⁸			—	—	0.15	0.02	—	—	0.21	0.27
Emery, 2000 ¹⁹			—	—	0.74	0.53	—	—	0.96	0.67
Ribbens, 2000 ²⁰			—	—	0.38	0.81	—	—	0.41	0.93
Lerndal, 2000 ²¹			—	—	—	—	—	—	1.00	1.10
Bathon, 2000 ²²			—	—	0.47	0.48	—	—	0.53	0.54
Hamilton, 2001 ²³			—	—	0.15	0.23	—	—	0.44	0.33
Cyclosporine										
Ahern, 1991 ²⁴	25	Trial	4.2	60.5	8.9	NR	50.0	53.0		
Van Rijthoven, 1991 ²⁵	28	Trial	5.0	56.7	6.4	76	55.0	44.0		
Lacki, 1994 ²⁶	9	Obs	2.5	NR	NR	NR	74.0	29.0		
Landewé, 1994 ²⁷	22	Trial	2.5	48.0	0.6	86	40.0	33.0		
Ferraccioli, 1996 ²⁸	10	Obs	3.0	54.0	0.7	NR	75.0	62.3		
Salaffi, 1996 ²⁹	12	Obs	2.5	50.5	6.4	67	47.6	50.0		
Salaffi, 1996 ²⁹	12	Obs	2.5	51.0	6.8	75	44.3	33.0		
Bendix, 1996 ³⁰	19	Trial	2.5	56.0	10.7	79	40.0	41.0		
Kim, 2000 ³¹	17	Trial	2.5	44.5	6.8	75	48.6	24.0		
Kim, 2001 ³²	34	Obs	2.5	42.6	8.7	76	39.0	19.0		

Table 1. Continued

	Week 4		Week 8		Effect Size Week 12		Week 16		Week 24	
	ESR	CRP	ESR	CRP	ESR	CRP	ESR	CRP	ESR	CRP
Felix-Davies, 1983 ⁴²	—	—	—	—	—	—	—	—	1.00	0.73
Neumann, 1983 ³³	0.05	0.03	0.32	0.15	0.67	0.32	0.62	0.62	—	—
Situnayake, 1990 ³⁵	—	—	—	—	—	—	—	—	0.78	0.47
van Rijthoven, 1991 ²⁵	—	—	—	—	—	—	—	—	0.48	0.33
Kim, 1997 ⁴³	—	—	—	—	—	—	—	—	0.63	0.23
Leflunomide										
Mladenovic, 1995 ⁴⁴	—	—	—	—	0.27	0.07	—	—	0.22	0.20
Smolen, 1999 ³⁸	—	—	—	—	—	—	—	—	0.29	0.55
Strand, 1999 ¹⁸	—	—	—	—	0.16	0.02	—	—	0.20	0.28
Emery, 2000 ¹⁹	—	—	—	—	0.44	0.43	—	—	0.44	0.45
Geborek, 2002 ⁴⁵	—	—	—	—	0.15	0.35	—	—	0.30	0.29
Kremer, 2002 ⁴⁶	—	—	—	—	—	—	—	—	0.08	0.39
	N	Design	Dose, mg/biweekly	Mean Age, yrs	Duration of RA, yrs	Proportion RF Positive	Mean ESR, mm/h	Mean CRP, mg/l		
Etanercept										
Moreland, 1999 ⁴⁷	78	Trial	25	53.0	11.0	79	34.7	47.0		
Weinblatt, 1999 ⁴⁸	59	Trial	25	48.0	13.0	84	28.4	29.0		
Bathon, 2000 ²²	207	Trial	25	51.0	1.0	87	37.9	33.0		
Geborek, 2002 ⁴⁵	165	Obs	25	54.0	14.9	NR	43.2	43.8		
Drynda, 2002 ⁴⁹	26	Obs	25	52.3	NR	58	66.5	52.4		
Catrina, 2002 ⁵⁰	60	Obs	25	53.0	NR	NR	47.9	42.5		
Infliximab										
			Dose, mg/kg							
Elliot, 1994 ⁵¹	24	Trial	10	50.6	7.3	75	63.1	64.0		
Lipsky, 2000 ⁵²	81	Trial	10	52.0	12.0	82	49.0	42.0		
Lipsky, 2000 ⁵²	87	Trial	10	54.0	11.0	82	50.0	33.0		
Geborek, 2002 ⁴⁵	135	Obs	3	55.4	14.1	NR	39.5	44.6		
Temekonidis, 2002 ⁵³	18	Obs	3	58.9	11.5	83	52.3	30.0		
Intramuscular gold										
			Dose, mg/wk							
Scott, 1989 ⁵⁴	32	Trial	50	54.7	2.0	71	54.8	46.6		
Situnayake, 1990 ³⁵	203	Obs	50	53.0	4.0	69	54.0	73.0		
Peltomaa, 1995 ³⁷	70	Obs	50	45.0	0.6	71	35.0	27.0		
Rau, 1997 ¹⁵	87	Trial	50	56.8	1.8	54	41.0	43.0		
Hamilton, 2001 ²³	72	Trial	50	58.0	6.0	64	44.0	46.2		
	Week 4		Week 8		Effect Size Week 12		Week 16		Week 24	
	ESR	CRP	ESR	CRP	ESR	CRP	ESR	CRP	ESR	CRP
Etanercept										
Moreland, 1999 ⁴⁷	—	—	—	—	0.26	0.22	—	—	0.23	0.24
Weinblatt, 1999 ⁴⁸	—	—	—	—	0.58	0.72	—	—	0.46	0.58
Bathon, 2000 ²²	—	—	—	—	0.56	0.55	—	—	0.51	0.52
Geborek, 2002 ⁴⁵	—	—	—	—	0.56	0.57	—	—	0.56	0.54
Drynda, 2002 ⁴⁹	0.69	0.80	—	—	0.83	0.78	—	—	0.72	1.00
Catrina, 2002 ⁵⁰	—	—	—	—	0.83	0.72	—	—	—	—
Infliximab										
Elliot, 1994 ⁵¹	0.74	0.80	—	—	—	—	—	—	—	—
Lipsky, 2000 ⁵²	—	—	—	—	—	—	—	—	0.21	0.54
Lipsky, 2000 ⁵²	—	—	—	—	—	—	—	—	0.64	0.25
Geborek, 2002 ⁴⁵	—	—	—	—	0.41	0.45	—	—	0.40	0.44
Temekonidis, 2002 ⁵³	—	—	0.57	0.47	—	—	0.44	0.61	0.35	0.61
Intramuscular gold										
Scott, 1989 ⁵⁴	—	—	—	—	—	—	—	—	1.72	1.16
Situnayake, 1990 ³⁵	—	—	—	—	—	—	—	—	0.56	0.56
Peltomaa, 1995 ³⁷	—	—	—	—	0.36	0.36	—	—	0.61	0.53
Rau, 1997 ¹⁵	—	—	—	—	0.39	0.58	—	—	0.58	0.54
Hamilton, 2001 ²³	—	—	—	—	0.42	0.40	—	—	0.55	0.56

Table 1. Continued

	Week 4		Week 8		Effect Size Week 12		Week 16		Week 24	
	ESR	CRP	ESR	CRP	ESR	CRP	ESR	CRP	ESR	CRP
Azathioprine										
Ahern, 1991 ²⁴	—	—	—	—	—	—	—	—	0.11	0.21
Jeurissen, 1991 ¹¹	—	—	—	—	—	—	—	—	0.41	0.65
Minocycline										
Kloppenborg, 1994 ⁶³	—	—	—	—	—	—	—	—	0.48	0.57
Prednisolone										
Stichtenoht, 1995 ⁶⁴	1.07	1.07	—	—	—	—	—	—	—	—
Combination treatment										
Scott, 1989 ⁵⁴	—	—	—	—	—	—	—	—	1.69	0.99
Nishiya, 1999 ⁶⁵	0.11	0.26	0.35	0.52	0.35	0.44	0.48	0.55	0.60	0.61
Pascalis, 1999 ⁶⁶	—	—	—	—	—	—	—	—	1.18	0.52
Rojkovich, 1999 ⁶⁷	—	—	—	—	—	—	—	—	1.31	0.41
Möttönen, 1999 ⁶⁸	—	—	—	—	1.04	0.53	—	—	1.09	0.55
Proudman, 2000 ³⁹	—	—	—	—	—	—	—	—	0.39	0.58
Marchesoni, 2002 ⁶⁹	—	—	—	—	—	—	—	—	0.72	0.66
Knijff-Dutmer, 2002 ⁴⁰	—	—	—	—	—	—	1.20	0.82	—	—

	N	Design	Dose	Mean Age, yrs	Duration of RA, yrs	Proportion RF Positive	Mean ESR, mm/h	Mean CRP, mg/l
Mixtures								
van der Heide, 1994 ⁷⁰	97	Trial	—	57.6	1.0	NR	40.0	32.0
ten Wolde, 1997 ⁷¹	53	Obs	—	59.9	10.6	77	28.0	15.0
Möttönen, 1999 ⁶⁸	98	Trial	—	48.0	0.7	66	39.0	33.6

	Week 4		Week 8		Effect Size Week 12		Week 16		Week 24	
	ESR	CRP	ESR	CRP	ESR	CRP	ESR	CRP	ESR	CRP
Mixtures										
van der Heide, 1994 ⁷⁰	—	—	—	—	0.37	0.38	—	—	0.55	0.52
ten Wolde, 1997 ⁷¹	—	—	—	—	0.22	0.15	—	—	—	—
Möttönen, 1999 ⁶⁸	—	—	—	—	0.95	0.56	—	—	1.00	0.60

Obs: observational study; NR: not reported.

0.54 and an effect size for ESR of zero. Excluding this study, the weighted paired effect size difference was 0.05 (95% CI -0.06, 0.17; $p = 0.39$), indicating ESR was slightly but not significantly more sensitive to change than CRP at this time point.

Effect size difference at 12 weeks. Among the 36 treatment arms (with 3913 patients) that reported results at 12 weeks, the pooled effect size of the ESR was 0.53 and the pooled effect size of the CRP was 0.44 (Table 2). The effect size of the ESR was larger than the effect size of the CRP in 20 of

Table 2. Pooled effect sizes for the ESR and CRP concentration, and the paired effect size difference, by study duration. Positive values of the paired effect size difference indicate that the ESR was more sensitive to change than the CRP, and negative values indicate that the CRP was more sensitive to change than the ESR. All values are weighted by sample size. P values represent tests of whether the paired effect size difference is different from zero (i.e., that the sensitivity to change of the ESR was different from that of the CRP).

Time	ESR Pooled Effect Size (95% CI)	CRP Pooled Effect Size (95% CI)	Paired Effect Size Difference(95% CI)	p
4 weeks (n = 8)	0.29 (0.10, 0.49)	0.39 (0.18, 0.60)	-0.05 (-0.11, 0.01)	0.11
8 weeks (n = 7)	0.41 (0.18, 0.64)	0.45 (0.29, 0.62)	-0.06 (-0.27, 0.15)	0.60
12 weeks (n = 36)	0.53 (0.43, 0.62)	0.44 (0.36, 0.53)	0.09 (0.03, 0.15)	0.005
16 weeks (n = 11)	0.65 (0.44, 0.87)	0.59 (0.47, 0.70)	0.11 (-0.02, 0.23)	0.13
24 weeks (n = 74)	0.59 (0.51, 0.67)	0.49 (0.44, 0.54)	0.11 (0.05, 0.17)	0.0004

the 36 treatment arms (56%). The weighted paired effect size difference was 0.09, indicating that the ESR was more sensitive to change than the CRP at this time point.

Effect size difference at 16 weeks. Among the 11 treatment arms (with 546 patients) that reported results at 16 weeks, the pooled effect size of the ESR was 0.65 and the pooled effect size of the CRP was 0.59 (Table 2). The effect size of the ESR was larger than that of the CRP in 7 of the 11 treatment arms (64%). The weighted paired effect size difference was 0.11, indicating that the ESR was more sensitive to change than the CRP at this time point, although the CI for this difference was wide and the difference was not significant.

Effect size difference at 24 weeks. Among 74 treatment arms (with 6232 patients) that reported results at 24 weeks, the pooled effect size of the ESR was 0.59 and the pooled effect size of the CRP was 0.49 (Table 2). Two small studies of cyclosporine reported very large effect sizes for the ESR, resulting in effect size differences that were much larger than those of other studies (1.64 and 2.43, respectively). These 2 outlier studies were not included in the pooled analysis. The effect size of the ESR was larger than the effect size of the CRP in 43 of the 74 treatment arms (58%). The weighted paired effect size difference was 0.11, indicating that ESR was more sensitive to change than CRP at this time point.

Evolution of responses over time. Thirty-one treatment arms reported results at both 12 weeks and 24 weeks, which allowed examination of whether differences favoring either

the ESR or CRP persisted or waned over time within a given study (Figure 1). In 9 of the 31 treatment arms, the paired difference in the effect sizes at 12 weeks was small (absolute value ≤ 0.04), and in each case the difference remained in this range at 24 weeks. In 12 treatment arms, the paired difference in the effect sizes at 12 weeks indicated the ESR was more sensitive to change than the CRP (≥ 0.05), and this difference persisted at 24 weeks in 8 of the 12 treatment arms. In 10 treatment arms, the paired difference in the effect sizes at 12 weeks indicated the CRP was more sensitive to change (≤ -0.05). At 24 weeks, 4 of these treatment arms favored the ESR rather than the CRP, and the effect was attenuated to near zero in 4 additional treatment arms. These findings suggest that in most treatment arms, differences present at 12 weeks tended to persist through 24 weeks, but in some treatment arms that indicated that the CRP was more sensitive to change early, this effect was lost by 24 weeks.

Association of patient characteristics and study characteristics on paired effect size differences. At Week 12, there were no associations between the effect size difference and mean patient age, mean duration of RA, proportion of seropositive patients in the study, mean ESR at study entry, year of publication, or whether the study was observational or a clinical trial. There was a significant inverse association between the effect size difference and the mean CRP at study entry (Spearman correlation $r = -0.43$; $p = 0.009$), indicating that treatment arms with higher mean CRP concentrations at

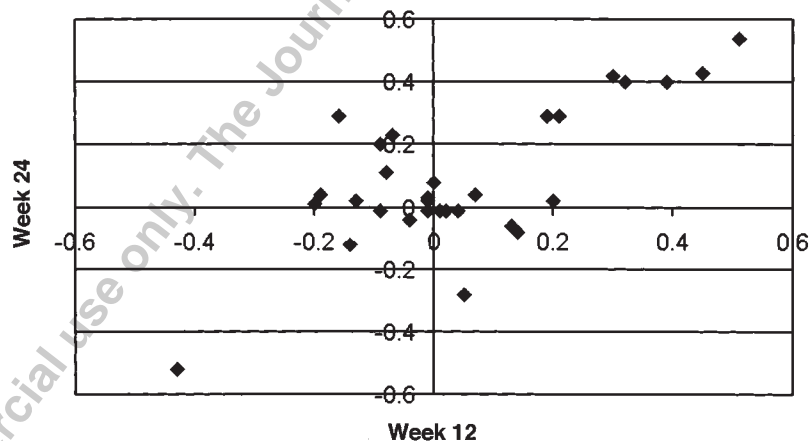


Figure 1. Relationship between paired effect size differences at Week 12 and Week 24 of treatment among studies that reported results at both time points. Positive effect size differences indicate ESR was more sensitive to change than CRP, while negative effect size differences indicate CRP was more sensitive to change than ESR. Values in the upper right quadrant indicate studies in which ESR was more sensitive to change than CRP at both Week 12 and Week 24. Values in the lower right quadrant indicate studies in which ESR was more sensitive to change than CRP at Week 12, but CRP was more sensitive to change at Week 24. Values in the lower left quadrant indicate studies in which CRP was more sensitive to change than ESR at both Week 12 and Week 24. Values in the upper left quadrant indicate studies in which CRP was more sensitive to change than ESR at Week 12, but ESR was more sensitive to change at Week 24. Values along the diagonal indicate similar results at Week 12 and Week 24.

baseline had a smaller difference between the effect size of the ESR and CRP (i.e., the sensitivity to change of the ESR and CRP was similar) than treatment arms with lower mean CRP concentrations. This was likely because treatment arms with higher baseline CRP concentrations had larger effect sizes for the CRP (Spearman $r = 0.47$; $p = .004$). The diversity of medications used and the small number of treatment arms did not allow meaningful comparisons of the paired effect size difference among medications at Week 12.

At Week 24, there were no significant associations between the effect size difference and patient age, duration of RA, the proportion of seropositive patients in the study, mean ESR or CRP at study entry, year of publication, or whether the study was observational or a clinical trial. However, there were significant differences among medications, with the CRP more sensitive to change than the ESR in studies of cyclosporine, and the ESR much more sensitive to change than the CRP in studies of sulfasalazine and combination therapy (Table 3).

DISCUSSION

In these studies of disease-modifying medications in RA, the ESR was more sensitive to change than the CRP at 12 weeks and 24 weeks of treatment. A difference of similar magnitude, favoring the ESR, was also present at 16 weeks of treatment. Considering the mean pooled effect size of 0.50 to 0.60 and a paired effect size difference of approximately 0.10, the sensitivity to change of the ESR is estimated to be 15% to 20% greater than that of the CRP. Few studies examined changes in these measures at times earlier than 12 weeks, and there was no clear difference in the sensitivity to change of the ESR and CRP at 4 weeks or 8 weeks of treatment. Among studies in which the ESR

responded faster than the CRP, this effect persisted through 24 weeks, while in studies in which the CRP responded faster than the ESR, this effect was often not maintained.

The ESR is affected by many factors other than systemic inflammation, including the patient's age, sex, and red blood cell morphology⁷². While these factors can confound comparisons of the ESR among patients, these factors would have little or no effect on comparisons of the ESR within individual patients, and so have less effect on the sensitivity to change of the ESR than might be anticipated. The ESR is also influenced by the hemoglobin concentration and by serum levels of immunoglobulins and rheumatoid factor⁷³. Because of these associations, the ESR may be considered a less specific measure of the acute phase response than the CRP. However, if the ESR also captures changes in hemoglobin, immunoglobulin, and rheumatoid factor concentrations with treatment, the association of the ESR with these other markers of inflammation may enhance its sensitivity to change.

The sensitivity to change of the ESR was not associated with its level at study entry, while the baseline concentration of CRP was associated with its sensitivity to change at 12 weeks. The sensitivity to change of the CRP was higher in studies with higher baseline CRP concentrations, suggesting that the sensitivity to change of the CRP is limited by ceiling effects more so than that of the ESR. The sensitivity to change of the CRP may also vary among different laboratory methods, such as immunodiffusion, nephelometry, fluorescent immunoassay, and rocket immunoelectrophoresis. Unfortunately, the method used to measure CRP was reported in only 21 of the 90 treatment arms (23%), and in only 18 treatment arms that reported data at 24 weeks, so our ability to detect differences in sensitivity to change

Table 3. Weighted paired effect size differences at 24 weeks, by medication.

	Medication	No. of Treatment Arms	Weighted Paired Effect Size Difference	95% CI
CRP more sensitive to change than ESR	Cyclosporine*	7	-0.32	-0.61, -0.03
	Azathioprine	2	-0.18	-0.64, 0.29
	Minocycline	1	-0.09	-0.66, 0.48
	Leflunomide	6	-0.08	-0.19, 0.03
	Etanercept	5	-0.03	-0.18, 0.13
	Infliximab	4	-0.01	-0.21, 0.19
	Chloroquine	2	-0.01	-0.48, 0.47
	Auranofin	3	0.03	-0.38, 0.44
	Intramuscular gold	5	0.06	-0.11, 0.23
	Hydroxychloroquine	2	0.10	-0.19, 0.40
	Methotrexate	15	0.15	0.05, 0.24
	Mixture	2	0.21	-0.05, 0.48
	Anakinra	2	0.22	-0.05, 0.49
ESR more sensitive to change than CRP	D-penicillamine	5	0.29	0.06, 0.52
	Sulfasalazine	6	0.37	0.22, 0.52
	Combination	7	0.45	0.28, 0.63

* Excluding 2 outlier studies.

among laboratory methods was limited. Similarly, the Westergren method was used to measure the ESR in 46 of the 90 treatment arms (51%), but the remaining studies did not report the method used to measure ESR.

The relative sensitivity to change of the ESR and CRP also varied among different medications, with studies of methotrexate, sulfasalazine, anakinra, D-penicillamine, and combination treatment indicating that the ESR was more sensitive to change than the CRP at 24 weeks. To be inclusive, studies of cyclosporine were used in the pooled analysis, even though this medication is recognized not to influence ESR⁷⁴. Inclusion of these studies would be expected to underestimate the sensitivity to change of the ESR relative to the CRP. Excluding studies of cyclosporine, the weighted paired effect size differences at Weeks 4, 8, 12, 16, and 24 were -0.05 ($p = 0.010$), 0.05 ($p = 0.39$), 0.09 ($p = 0.005$), 0.14 ($p = 0.03$), and 0.12 ($p = 0.0002$), demonstrating slightly larger differences in favor of the ESR.

Although a large number of treatment arms were analyzed, many studies that reported having collected both the ESR and CRP did not include data on both tests. Other studies reported the data incompletely or reported median changes, which did not permit the calculation of effect sizes. Most of the excluded studies had small samples, and therefore would have contributed relatively little to the weighted results, but it is unclear how these studies might have influenced the paired effect size differences. Publication bias may have influenced our results if both tests were performed in a particular study but only the test that improved with treatment was reported. Of the 12 studies that were excluded because either the ESR or the CRP data were missing, 8 studies did not report CRP data. Therefore, any publication bias might favor the CRP, and would have caused us to underestimate the sensitivity to change of the ESR relative to that of the CRP. Few studies reported changes in these laboratory tests shortly after the start of treatment, which limited our ability to examine early differences in sensitivity to change.

A previous comparison found that the ESR and CRP performed similarly in detecting patients with RA who met the preliminary American College of Rheumatology improvement criteria, which require a 20% improvement in the measure of the acute phase reactant⁷⁵. While this modest requirement may be satisfied equally well by both measures, the results of this pooled analysis suggest that the ESR would be better able to detect changes than the CRP. The ESR may therefore be the preferred measure of the acute phase response in RA when more stringent criteria for response are used.

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