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COBRA Combination Therapy in Patients With Early Rheumatoid Arthritis

Long-Term Structural Benefits of a Brief Intervention

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Objective. **The Combinatietherapie Bij Reumatoide Artritis (COBRA) trial demonstrated that step-down combination therapy with prednisolone, methotrexate, and sulfasalazine (SSZ) was superior to SSZ monotherapy for suppressing disease activity and radiologic progression of rheumatoid arthritis (RA). The current study was conducted to investigate whether the benefits of COBRA therapy were sustained over time, and to determine which baseline factors could predict outcome.**

Methods. **All patients had participated in the 56-week COBRA trial. During followup, they were seen by their own rheumatologists and were also assessed regularly by study nurses; no treatment protocol was specified. Disease activity, radiologic damage, and functional ability were the primary outcome domains. Two independent assessors scored radiographs in sequence according to the Sharp/van der Heijde method. Outcomes were analyzed by generalized estimating equations on the basis of intent-to-treat, starting with data obtained at the last visit of the COBRA trial (56 weeks after baseline).**

Results. **At the beginning of followup, patients in the COBRA group had a significantly lower mean time-averaged 28-joint disease activity score (DAS28) and a significantly lower median radiologic damage (Sharp) score compared with those in the SSZ monotherapy group. The functional ability score (Health Assessment Questionnaire [HAQ]) was similar in both groups. During the 4–5 year followup period, the time-averaged DAS28 decreased 0.17 points per year in the SSZ group and 0.07 in the COBRA group. The Sharp progression rate was 8.6 points per year in the SSZ group and 5.6 in the COBRA group. After adjustment for differences in treatment and disease activity during followup, the between-group difference in the rate of radiologic progression was 3.7 points per year. The HAQ score did not change significantly over time. Independent baseline predictors of radiologic progression over time (apart from treatment allocation) were rheumatoid factor positivity, Sharp score, and DAS28.**

Conclusion. **An initial 6-month cycle of intensive combination treatment that includes high-dose corticosteroids results in sustained suppression of the rate of radiologic progression in patients with early RA, independent of subsequent antirheumatic therapy.**

Rheumatoid arthritis (RA) is a chronic, potentially disabling disease characterized by inflammation of the joints, periarticular bone resorption and cartilage

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destruction, and extraarticular manifestations. Mortality of RA patients with long-term disease is increased compared with that of the general population (1).

Currently, RA is treated aggressively and as early as possible with disease-modifying antirheumatic drugs (DMARDs), because this approach has proven to be better than the stepwise approach of carefully introducing consecutive DMARDs of increasing potential (2–4). Several reports have suggested that treatment with combinations of DMARDs, as compared with DMARD monotherapy, suppresses disease activity more thoroughly and retards radiologically measured damage to cartilage and bone (5–7).

One such report is from the Combinatietherapie Bij Reumatoide Artritis (COBRA) trial, in which COBRA combination therapy was compared with sulfasalazine (SSZ) monotherapy in patients with early RA who had never taken DMARDs (8). COBRA combination therapy involved prednisolone (initially 60 mg/day, tapered in 6 weekly steps to 7.5 mg/day, then stopped after week 28), low-dose methotrexate (MTX; 7.5 mg/week, then tapered and stopped after week 40), and SSZ maintenance therapy (2 gm/day). Results from the 56-week trial showed that COBRA combination therapy was more efficacious than SSZ monotherapy with respect to suppressing disease activity and slowing radiographic progression. Another important finding was that radiologic progression during the first 1.5 years was significantly slower in the COBRA group than in the SSZ monotherapy group. This observation fits the theory that thorough suppression of disease activity during the first phase of RA may result in sustained inhibition of the rate of radiologic progression. Sustained suppression of radiologic progression is important, because radiologic damage is related to the long-term outcome of RA patients (e.g., functional disability) (9). Until now, however, evidence that outcome can be modified by early aggressive intervention has been lacking.

The current report describes results of the 5-year followup study of patients in the COBRA trial. The main objective of this followup study was to investigate whether patients who had been randomized to the COBRA treatment group differed from those randomized to the SSZ group with respect to 3 important outcome domains: disease activity, radiologic damage, and functional ability. A second objective was to establish whether the rate of radiologic progression was influenced by the primary intervention rather than by differences in DMARD treatment and/or disease activity after the end of the double-blind COBRA study.

PATIENTS AND METHODS

Patients. All patients in the current study participated in the COBRA study, a multicenter, randomized, double-blind, controlled trial of 56 weeks duration in which COBRA combination therapy was compared with SSZ monotherapy. Details of that study have been reported previously (8).

Inclusion criteria for the original COBRA study (entry between May 1993 and May 1995) were active RA ($\geq$6 actively inflamed joints in $\geq$3 of 18 joint groups [1 large joint or 1 group of small joints]) as well as 2 of the following: tender joint count $>$9, early morning stiffness $>$45 minutes, or Westergren erythrocyte sedimentation rate (ESR) $>$28 mm/hour, all for $<$2 years duration. Prior treatment with DMARDs (except hydroxychloroquine, which was allowed) or corticosteroids was not allowed. All patients were invited to participate in the COBRA followup study. In keeping with the original protocol, blinded treatment was continued until week 80 whenever possible. During the followup period, the treating rheumatologists were allowed to select therapy for individual patients, with no limiting regulation. They could either continue treatment with SSZ, replace SSZ with any other DMARD or combination of DMARDs, add corticosteroids, repeat COBRA treatment in patients who had been randomized to the COBRA group, or start COBRA treatment in patients randomized to the SSZ group. The length of the followup period was considered to be indefinite, but followup data for the current analysis were censored on May 1, 1999. Only patients with at least 3 sets of radiographs available from the first year of COBRA treatment (including the 1-year time point) were included.

Intervention. COBRA combination therapy is a step-down DMARD strategy consisting of 1) an oral pulse of prednisolone followed by low-dose maintenance therapy until week 28 (60 mg/day, 40 mg/day, 25 mg/day, 20 mg/day, 15 mg/day, and 10 mg/day for weeks 1, 2, 3, 4, 5, and 6, respectively, then 7.5 mg/day for 6 more weeks, followed by complete withdrawal); 2) low-dose MTX (7.5 mg/week) for 40 weeks followed by withdrawal; and 3) a maintenance dosage of SSZ (2 gm/day). All patients received folic acid (1 mg/day) and calcium (500 mg/day); 25-hydroxyvitamin D (400 IU/day) was given as necessary. Patients randomized to the SSZ monotherapy group received a maintenance dosage of SSZ (2 gm/day), placebo tablets (representing prednisolone and MTX), as well as the vitamin supplements described above. According to the trial protocol, all patients should have been receiving SSZ maintenance therapy at week 56. However, during the second half-year of the study, patients who experienced a disease flare (according to prespecified criteria) during or after tapering could restart treatment with the drug that was most recently withdrawn.

Outcome measurements. *Disease activity and functional ability.* During both the double-blind trial and the followup phase, disease activity was measured regularly by trained research nurses who were not involved in any treatment decisions. During the followup study, measurements were taken at least once a year but in some cases more frequently. Disease activity was measured using the World Health Organization/International League of Associations for Rheumatology core set of end points (10). The measures relevant to the followup study included a tender joint count (68 joints), a swollen joint count (48 joints; modified from the American

College of Rheumatology 66-joint count) (10); pain (according to a 100-mm visual analog scale [VAS], with "worst imaginable" and "no pain" as extremes); functional ability (the Dutch-modified version of the Health Assessment Questionnaire [HAQ] [13], with scores ranging from 0 for "best" to 3 for "worst"); patient's and assessor's global assessment of disease activity (100-mm VAS, with "very severe disease activity" and "no disease activity" as extremes); and ESR (Westergren method).

In the current study, disease activity is reported in the form of the 28-joint Disease Activity Score (DAS28), a validated composite index measuring the swollen joint count (28 joints), tender joint count (28 joints), ESR, and the patient's overall assessment of well-being (11,12). Because other joint counts were used in the original trial, the 28-joint counts for swollen and tender joints were recalculated from the source data at the individual joint level. Functional disability was measured with the 24-item HAQ (13).

Radiologic progression. During the double-blind phase of the original COBRA study, radiographs of the hands and feet were obtained at 6-month intervals. The followup study protocol recommended performing radiography of the hands and feet once a year. In addition, all patients were invited to undergo radiography at the end of the followup trial (first 3 months of 1999) in an attempt to obtain radiographs of all patients 4–6 years after they started treatment.

Radiographic damage was scored by 2 blinded observers (AB and ACV) according to the Sharp/van der Heijde method (14). This method measures erosions and joint space narrowing in 44 different joints and provides an aggregated sum score ranging from 0 to 448. All radiographs were presented to the observers in chronological order so that each set could be compared with the previous one. Total scores could increase or be stable but could not decrease (improve). Results are reported as the mean value of scores reported by the 2 observers.

DMARD use. At each visit, the research nurse who measured disease activity also collected information on each patient's current and previous use of DMARDs, corticosteroids (oral, parenteral, or intraarticular), and nonsteroidal antiinflammatory drugs, as well as concomitant use of any medication unrelated to RA. The nurse recorded the dosage of each DMARD that was being used at the time of a particular visit. A patient was considered to be taking DMARDs and/or prednisolone at a particular visit if he or she was receiving these drugs at that time. If the patient reported having used these drugs at some time between 2 visits, he or she was noted to have been taking them at the first of the 2 time points and not at the second.

Analysis. Explorative analysis included use of scatter plots to visualize the course of the different scores of the treatment groups over time and simple linear regression to fit the course of the 3 primary outcome measures (DAS28, total radiologic damage score, and HAQ score). Longitudinal data sets are characterized by observations with high variability between patients and rather low variability within patients (i.e., the radiologic damage score at 1 year is highly correlated with the radiologic damage score at time 0). Because of the high within-patient correlation, longitudinal relationships cannot be analyzed with ordinary regression methods.

Generalized estimating equations (GEE) is a regression technique for studying intervariable relationships in observational longitudinal studies; this technique takes into account time, as well as time-independent and time-dependent covariates (15). The advantages of GEE over other methods are that GEE uses all available longitudinal data, allows unequal numbers of repeated measurements and unequal time intervals, and does not require multivariate normality of the outcome variable. GEE does require an a priori "working" correlation structure in order to adjust for the within-subject correlation operating in repeated-measurement designs. A correlation structure must be chosen on the basis of the actual data set. In this study, the "exchangeable" correlation structure was appropriate for all 3 outcome measures, because in the correlation matrix, all correlations at different time points were approximately equal (0.75–0.90).

Table 1. Baseline characteristics of sulfasalazine (SSZ) and COBRA treatment groups*

	SSZ n = 74	COBRA n = 74
Age, years, mean ± SD	50 ± 13	50 ± 12
% male/% female	47/53	35/65
Disease duration, years, median (25th, 75th percentile)	0.3 (0.2, 0.7)	0.3 (0.2, 0.5)
Rheumatoid factor, % positive	71	76
HLA–DR4 status, % positive	55	59
Radiologic damage score at baseline, median (25th, 75th percentile)	5 (1, 10)	3 (1, 9)
DAS28 at baseline, mean ± SD	6.1 ± 1.1	6.2 ± 1.1
HAQ score at baseline, mean ± SD	1.4 ± 0.7	1.5 ± 0.7
No. of observations, starting at 1 year, total [median no./patient] (range)		
Radiographs	326 [4] (3–7)	353 [4] (3–7)
DAS	345 [5] (3–10)	358 [5] (3–9)
HAQ scores	399 [5] (3–9)	426 [5] (3–9)
Years of followup from year 0, median (range)	4.5 (3.0–6.0)	4.5 (2.5–6.0)

* COBRA treatment = prednisolone + methotrexate + sulfasalazine; DAS28 = 28-joint Disease Activity Score; HAQ = Health Assessment Questionnaire.

Baseline variables (determinants of outcome) introduced into the model were age at the start of study, sex, disease duration at the start of study (in months), rheumatoid factor (RF) (present or absent), HLA–DR4 status (negative, heterozygous, homozygous), total radiologic damage score, DAS28 at the start of study, and ESR at the start of study. Longitudinal variables were use of SSZ, prednisolone, MTX, or prednisolone plus MTX at various specific time points (yes or no), and use of any combinations of DMARDs at various specific time points (yes or no). Actual dosages of all DMARDs used during followup were recorded.

The DAS28 measures disease activity, and the time-averaged DAS28 measures "historic disease activity." The justification for using the time-averaged measure instead of a cross-sectional measure of disease activity is that the former correlates better with radiologic progression (3,16,17). The time-averaged DAS28 was calculated at each time point (e.g., time point X) by dividing the area under the DAS28 time curve (from time 0 to time X) by X. The effect of treatment (SSZ monotherapy or COBRA) on the course of the DAS28, radiologic damage score, and HAQ score was investigated by introducing the interaction term "treatment × time" in the GEE model. Interaction was simultaneously adjusted for the main effects in all cases. Based on the assumption that all prognostic variables for outcome are equally divided among both groups by randomization, the regression coefficient obtained for the treatment × time interaction reflects the average annual difference in radiologic progression between groups.

The effects of all potential baseline determinants on the relationship between treatment group and radiologic progression were studied making use of the hierarchical backward elimination principle. This means that all variables were investigated separately with respect to their potential to modify the relationship between treatment group and outcome measurement (effect modification) and to influence the magnitude of the regression coefficient obtained for this relationship (confounding). Baseline variables that changed the regression coefficient at least 10% were considered confounders.

RESULTS

The COBRA trial included 156 patients, 1 of whom withdrew during the first week because of spontaneous remission before the start of therapy. Seven of the remaining 155 patients were lost to followup for 2 reasons: <3 sets of radiographs available from the first year (4 patients) and withdrawal of 1 site investigator (3 patients). Table 1 summarizes the most important characteristics of the remaining 148 patients (74 SSZ, 74 COBRA). The 2 groups were reasonably well matched with respect to demographic variables, factors related to the severity of RA (RF positivity, HLA–DR4 status), DAS28, HAQ score, and radiologic damage score. The total number of outcome observations and the median duration of followup per patient were similar in the 2 groups.

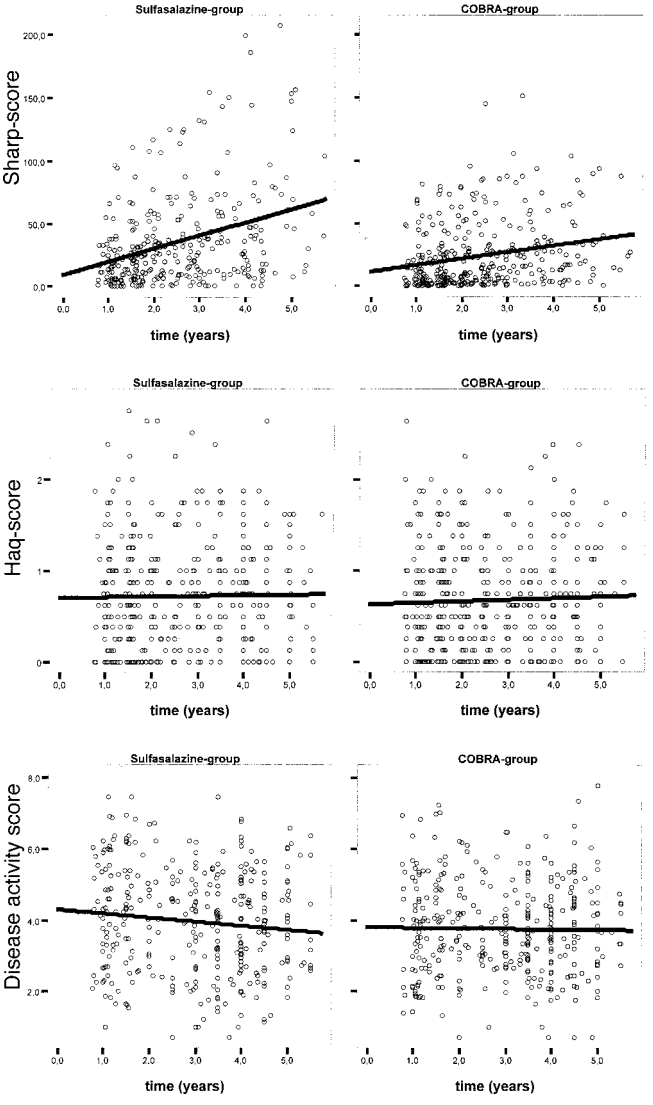

Figure 1. Scatter plots of individual Disease Activity Scores, Sharp damage scores, and Health Assessment Questionnaire (HAQ) functional disability scores over time during followup. Each symbol represents one observation. All observations were made in 148 patients. COBRA = prednisolone + methotrexate + sulfasalazine.

Outcome. Figure 1 shows the actual outcome scores plotted against time for all 3 outcome variables, beginning 1 year after the start of the COBRA trial. At first glance, it is clear that the DAS28 and the HAQ score were similar and relatively stable over time in both groups. The DAS28 seemed to decrease slightly in the SSZ group but also started from a somewhat higher level. As an illustration, a typical patient with a DAS28 of 4.0 (which was the average DAS28 during followup) has a swollen joint count of 3, a tender joint count of 6,

Table 2. Long-term outcomes in the SSZ and COBRA treatment groups*

	Score at 1 year†	Mean change per year	*P*	Difference between groups (95% CI) (*P*)
Radiologic damage				
SSZ	17 (5.8, 29)	8.6 (6.2, 11)	0.001	3.0 (0.2, 5.8) (0.033)
COBRA	6.5 (2.0, 21)	5.6 (4.3, 7.1)	0.001	
Disease activity				
DAS28				
SSZ	4.3 ± 1.6	−0.13 (−0.24, −0.02)	0.021	0.10 (−0.06, 0.26) (0.265)
COBRA	3.7 ± 1.4	−0.02 (−0.12, 0.08)	0.629	
Time-averaged DAS28				
SSZ	4.8 ± 1.3	−0.17 (−0.23, −0.11)	0.001	0.09 (0.01, 0.15) (0.014)
COBRA	4.2 ± 1.2	−0.07 (−0.11, −0.03)	0.001	
Functional ability				
SSZ	0.72 ± 0.60	0.01 (−0.03, 0.05)	0.647	0.00 (−0.04, 0.04) (0.875)
COBRA	0.69 ± 0.61	0.01 (−0.03, 0.05)	0.745	

* Outcome measures for radiologic damage and functional ability were the Sharp score and HAQ score, respectively. Change scores are longitudinal (time) trends per group, estimated using generalized estimating equations (GEE) (see Patients and Methods). Differences between groups are differences in time trends calculated using GEE with interaction terms (see Patients and Methods). Differences are not adjusted for other predictors of outcome. 95% CI = 95% confidence interval (see Table 1 for other definitions).
† Values for the Sharp score are the cross-sectional median (25th, 75th percentiles); other values are the mean ± SD.

and an ESR of 11 mm/hour; another example of a DAS28 of 4.0 is a swollen joint count of 1, a tender joint count of 4, and an ESR of 33 mm/hour. Therefore, a DAS28 of 4.0 translates to low-to-moderate disease activity, which apparently is the mean result of the treatment chosen for these patients. In contrast to these clinical scores, the radiologic damage score increased progressively over time in both groups and was substantially higher in the SSZ group.

The scatter plots show trends but do not allow between-group statistical inference. Such plots also do not take into account the effect of within-patient correlation of repeated measurements. Table 2 summarizes the GEE analysis of the long-term effects of COBRA and SSZ treatment on radiologic damage, disease activity, and functional disability. Because the COBRA trial had a fixed treatment protocol of ~1 year (56 weeks), the analysis of long-term effects started at 1 year. At that time, patients in the COBRA group had a significantly lower Sharp score, DAS28, and time-averaged DAS28 ($P = 0.009$, $P = 0.027$, and $P = 0.003$, respectively), compared with patients in the SSZ group. The HAQ score was similar in both groups (~0.70), which is in accordance with mild disability and substantial improvement compared with the score of 1.5 at the start of the COBRA trial.

In both groups, the Sharp damage score increased significantly over time. However, the mean change per year was 35% lower in the COBRA group (5.6 points versus 8.6 in the SSZ group; $P = 0.03$) (Table 2). Thus, the projected Sharp score at 5 years was 51 in the SSZ group, compared with 29 in the COBRA group. The effect of COBRA therapy versus SSZ was approximately similar with respect to the erosion score (increase of 4.7 points/year in the SSZ group versus 3.3 in the COBRA group [30% reduction]) and the joint space narrowing score (increase of 3.8 points/year in the SSZ group versus 2.2 in the COBRA group [42% reduction]). The projected erosion scores at 5 years were 31 in the SSZ group and 17 in the COBRA group. The projected joint space narrowing score at 5 years was 20 in the SSZ group, compared with 11 in the COBRA group.

Using GEE, we investigated whether radiologic progression during the 56-week trial period differed from radiologic progression thereafter. During the trial period, the mean Sharp score increased 12.4 points/year in the SSZ group and 6.6 points/year in the COBRA group, compared with 8.6 and 5.6 points/year, respectively, thereafter. This analysis shows that radiologic progression in the COBRA group did not resume after the trial. During the observation period, 5 patients in the SSZ group and 14 in the COBRA group had no radiologic progression, defined as a mean increase in Sharp score of <1 point/year ($P = 0.049$ by chi-square test).

The DAS28 remained constant in the COBRA group and showed a small but statistically significant decrease over time in the SSZ group. Time-averaged DAS28 decreased slightly over time in both groups, but the decrease in the SSZ monotherapy group was greater. Assuming a constant difference of 0.10 points/year, it can be calculated that the difference of 0.6 in time-averaged DAS28 at 1 year will be lost at 7 years (i.e.,

Table 3. Use of disease-modifying antirheumatic drugs (DMARDs) and combinations of these drugs at 2 time points during followup*

	At start of followup		At 5 years of followup	
	SSZ	COBRA	SSZ	COBRA
DMARD therapy	97	98	96	96
Including SSZ	69	77	32	45
Including methotrexate (MTX)	10	11	32	34
Including prednisolone	10	16	13	18
Any combination of DMARDs	8	16	12	23
Including prednisolone + MTX	4	8	5	14
Including COBRA	0	3	0	2

* Prednisolone is considered a DMARD. Values are the percent of patients. See Table 1 for other definitions.

after 6 years of followup). After the large improvement during the trial period, the HAQ score remained stable in both groups during followup. Adjustment for cross-sectional DAS28 did not change the results.

DMARD use during followup. Table 3 shows the distribution of treatments among patients in the 2 groups at the start of followup. At 1 year, almost all patients used at least 1 DMARD. Most patients (73%) were receiving SSZ treatment. Prednisolone was used by 13% of patients; 6% used it in combination with MTX, 3% (2 patients in the COBRA group) used it as part of COBRA therapy, 2% used it in combination with SSZ, and 4% used prednisolone in combination with other DMARDs. None of the patients used prednisolone as monotherapy. Eleven percent of patients were taking MTX. One percent of patients used antimalarial drugs, 5% used intramuscular gold, and 1% used D-penicillamine (data not shown). Three percent of patients did not use any DMARDs or prednisolone. There were no significant differences in DMARD use between groups at the start of followup, but the proportion of patients using prednisolone was somewhat higher in the COBRA group (16% versus 10% in the SSZ group), as was the proportion of patients using any form of DMARD combination therapy (16% versus 8% in the SSZ group).

During followup, many patients who had been receiving SSZ began taking a different DMARD instead, often MTX. Only 3 patients started using intramuscular gold as a DMARD at some time point during followup, and 2 patients started taking D-penicillamine. Azathioprine, cyclosporin A, and cyclophosphamide were each started by 1 patient during followup. The number of patients receiving MTX increased from 11% at 1 year to 33% at 5 years. The difference in prednisolone use between groups remained constant at 5 years (SSZ 13% versus COBRA 18%). Use of MTX plus prednisolone increased over time; at 5 years, 5% of the SSZ group and 14% of the COBRA group used this particular combination, and the difference in time trend was statistically significant ($P = 0.033$; see below). During followup, restarts of true COBRA therapy were rare (1 in the SSZ group, 2 in the COBRA group). An additional 5 patients (2 SSZ, 3 COBRA) started using the combination of SSZ/MTX/prednisolone during followup, but the maintenance doses of prednisolone were lower than those used during the COBRA trial. Not all of these patients still used this combination at 5 years.

A comparison of DMARD use among both groups during followup is crucial for interpreting the long-term effects of COBRA therapy on radiologic progression. GEE for binary responses (expressed as the chance of being treated with any particular drug at a certain time point) allowed investigation of time trends in DMARD use (18), and the same pattern as outlined above emerged. The chance of being treated with SSZ decreased significantly over time and similarly in both groups (SSZ, odds ratio [OR] of being treated with SSZ 0.68, $P = 0.0001$, for each year of followup; COBRA, OR 0.67, $P = 0.0001$ per year). The chance of being treated with MTX increased significantly over time and similarly in both groups (OR 1.53 in the SSZ group versus 1.52 in the COBRA group, $P = 0.0001$ for both groups). The chance of being treated with prednisolone did not change significantly in either group (OR 1.02 in the SSZ group versus 1.06 in the COBRA group), as was the case for any DMARD combination (OR 1.15 in the SSZ group versus 1.09 in the COBRA group). The chance of being treated with MTX plus prednisolone, however, was significantly lower in the SSZ group (OR 0.89, $P = 0.508$) than in the COBRA group (OR 1.33, $P = 0.006$) (between-group difference, $P = 0.033$). The chance of being treated with the COBRA combination was similar in both groups (OR 1.08 in the SSZ group versus 1.17 in the COBRA group).

The dosages of SSZ, MTX, and prednisolone did not differ significantly between groups at 1 year (SSZ, mean ± SEM 1,925 ± 38 mg/day in the SSZ group versus 1,924 ± 28 in the COBRA group; MTX, 11.0 ± 0.7 mg/week versus 10.3 ± 0.6; and prednisolone, 6.8 ± 0.6 mg/day versus 6.2). Among patients who used SSZ, the dosage remained approximately stable over time in both groups (β score + 0.43 mg/week/year, $P = 0.09$). The dosage of prednisolone remained stable in both groups (β score + 0.01 mg/day/year, $P = 0.8$). Because time trends and mean dosages were not different between groups, we did not calculate cumulative DMARD doses over time.

Table 4. Radiologic progression by time, with adjustment for confounders*

Time	No. patients/no. observations	No. observations per patient	True progression rate (points/year)		Between-group difference (95% confidence interval) (*P*)	
			SSZ	COBRA	Unadjusted	Adjusted
From 0.5 years	148/798	5	9.3 (1.3)	5.7 (0.8)	3.6 (0.7, 6.6) (0.015)	3.4 (0.4, 6.4) (0.021)
From 1.0 years	146/679	4	8.6 (1.2)	5.6 (0.7)	3.0 (0.2, 5.8) (0.033)	3.7 (0.5, 6.9) (0.018)
From 1.5 years	141/523	4	8.4 (1.2)	5.1 (0.7)	3.3 (0.5, 6.3) (0.019)	5.6 (1.6, 9.6) (0.004)
From 2.0 years	141/394	3	8.3 (1.3)	4.9 (0.7)	3.4 (0.4, 6.4) (0.023)	5.8 (0.8, 10.8) (0.023)

* Adjusted for baseline variables (age, sex, disease duration at baseline, DAS28 at baseline, Sharp score at baseline, rheumatoid factor status at baseline, HLA–DR4 status) and longitudinal variables (SSZ use, prednisolone use, methotrexate [MTX] use, prednisolone + MTX use, use of combination therapy with disease-modifying antirheumatic drugs, time-averaged DAS28). See Table 1 for other definitions.

Sensitivity analysis. In order to test the robustness of estimates of the rate of radiologic progression, we also analyzed the data at starting points other than 1 year (Table 4). As expected, the rate of radiologic progression depended on the chosen starting point: the later the start of analysis, the lower the rate of progression, which is consistent with a decrease in the rate of radiologic progression over time (Table 3). However, the between-group differences were independent of the time point at which the analysis started. Adjustment for cross-sectional baseline variables, as well as for the longitudinally obtained variables regarding DMARD use and disease activity, did not seriously threaten the stability of the estimate for the between-group difference; adjustment only accentuated the difference (Table 3). Thus, we concluded that the effect of COBRA therapy could not be explained by differences in DMARD use or disease activity, or by differences in the presence of baseline predictors for radiologic progression.

The relative contribution of the longitudinal variables to the explained variance in observed radiologic damage (estimated R^2 0.63). In the "full" model, use of MTX during followup was significantly associated with a *higher* radiologic damage score ($\beta = 17$, $P = 0.002$), whereas the combination of MTX plus prednisolone was associated with a *lower* radiologic damage score ($\beta = -16$, $P = 0.033$).

We also investigated the long-term effects of COBRA (adjusted for DMARD use during followup) on disease activity (DAS28) over time and on the time-averaged DAS28. The difference between the COBRA group and the SSZ monotherapy group with respect to time-averaged DAS28, 0.06, was no longer statistically significant (95% confidence interval [95% CI] −0.01, 0.13). Continuous SSZ treatment during followup was associated with a *lower* time-averaged DAS28 ($\beta = -0.15$, $P = 0.007$), whereas MTX treatment during followup was associated with a *higher* time-averaged DAS28 ($\beta = 0.17$, $P = 0.007$).

There were also no significant differences between the COBRA group and the SSZ monotherapy group with respect to the HAQ score over time (after adjustment for DMARD use) and disease activity over time (difference 0.01 [95% CI −0.05, 0.07]). DMARD use during followup was not associated with the HAQ score during followup.

Prediction of outcome. To identify baseline factors that independently predicted long-term outcome, we made use of the entire COBRA data set. Outcome measures of interest were the radiologic damage score, the time-averaged DAS28 (as a measure for burden of illness), and the HAQ score (as a measure for functional disability).

Table 5 shows the predictive contribution of each factor if introduced separately in the GEE model (unadjusted), as well as those factors that contribute independently to the outcome of interest (adjusted). Apart from treatment allocation, the mean rate of radiologic progression over time can also be predicted by knowing the patient's RF status (mean rate of progression is 3.6 points higher per year if RF positive), the baseline Sharp score (0.20 points higher per year for each additional point at baseline), and baseline DAS28 (progression rate 1.2 points higher per year per DAS28 point). Importantly, disease duration at the start of the trial (1–24 months) did not predict radiologic progression. The estimated model R^2 is 0.67.

A high time-averaged DAS28 at the end of followup was significantly associated with a high DAS28 at baseline ($\beta = 0.44$ [95% CI 0.26–0.62]; data not shown) but not with treatment allocation (linear regression analysis with transformation of variables not normally distributed, instead of GEE). A high HAQ score during followup was significantly associated with higher

Table 5. Predictors of long-term radiologic progression*

	Regression coefficient			
	Unadjusted (95% CI)	*P*	Adjusted (95% CI)	*P*
Treatment allocation, SSZ vs. COBRA	−3.6 (−6.4, −0.8)	0.009	−3.2 (−5.6, −0.8)	0.010
Rheumatoid factor status, positive vs. negative	4.5 (1.5, 7.5)	0.002	3.6 (1.2, 5.0)	0.004
Sharp score at baseline, per point (0–448)	0.20 (0.09, 0.31)	0.001	0.20 (0.08, 0.32)	0.001
DAS at baseline, per point (0–9.1)	1.1 (−0.1, 2.2)	0.072	1.2 (0.2, 2.2)	0.050
Age at baseline, per year	0.07 (−0.05, 0.19)	0.250	0.06 (−0.06, 0.18)	0.288
Sex, male vs. female	0.63 (−2.4, 3.6)	0.684	0.82 (−1.90, 3.58)	0.551
Disease duration at baseline, per month	0.00 (−0.21, 0.22)	0.890	−0.04 (−0.28, 0.20)	0.720
HLA–DR4 status, homozygous/heterozygous vs. absent	0.09 (−1.91, 2.09)	0.930	−0.45 (−1.35, 0.45)	0.591

* Regression coefficients describe the interaction between the variables and time and represent the development of radiologic progression per year with respect to that variable. In the full model, interactions are tested under the adjustment for main effects and time. 95% CI = 95% confidence interval. See Table 1 for other definitions.

age at baseline ($P = 0.027$) and longer disease duration ($P = 0.001$) but not with treatment allocation ($P = 0.707$) or radiologic damage ($P = 0.684$) (data not shown).

DISCUSSION

This study shows that use of intensive, short-term combination treatment in patients with very early RA (according to the COBRA schedule) induced a sustained reduction of the rate of radiologic progression (35%) compared with that induced by the active comparator, SSZ monotherapy. This reduction of radiologic progression could not be explained by differences in consecutive DMARD therapy, including differences in DMARD dosages, or differences in disease activity after the first year. After COBRA therapy was stopped at the end of the trial, radiologic progression did not resume but stabilized at a level that was lower than that reached in the SSZ monotherapy group.

These observations support the concept that the rate of radiologic progression is set during the very early stages of RA, and that pharmacologic resetting of the radiologic progression rate is easiest to achieve within a narrow time frame, called the "window of opportunity" (19). Once the rate of progression is established, a difference in the rate at the group level remains detectable after a number of years, independent of subsequent therapies. This conclusion is valid with regard to the mean level of disease activity (and thus treatment intensity) seen in the followup period. It is not clear whether the same difference in the radiologic progression rate would have occurred if disease activity during followup was further suppressed, to a level such as that seen in clinical remission.

Several features of this study may serve to increase confidence in the results. Randomization successfully created groups that were initially similar in terms of prognosis; the followup data were rich and complete, with a median of 4 observations for 148 of the initial 155 patients, and analysis was by GEE on the basis of intent-to-treat. A potential weakness of the study was the lack of treatment protocol in the followup period. Fortunately, treatment and resulting disease activity were similar in both groups, yielding extra power to detect the long-term effect of COBRA therapy. Radiographs were assessed independently by the 2 observers who also read the initial radiographs. These were read in sequence, which increases sensitivity to change but may bias the results upward (20). We believe this is not a problem, because any bias affects both groups.

This study addresses 3 different domains of outcome in RA: disease activity, radiologic damage, and functional ability. Irreversible functional disability is thought to be the long-term result of unchecked progression of radiologic damage. However, the HAQ score was stable in both groups during followup, and we found no relation between radiologic damage and HAQ score. This finding is in accordance with results of other studies that have shown that the HAQ score, at least at the group level, does not increase during the first decade of RA (9). A recently recognized problem is that the HAQ may measure disease activity along with disability until late in the disease (21,22). We also found a strong longitudinal association between HAQ and DAS28 after

the first year of observation (data not shown). Adjustment for the DAS28 did not change the net effects of SSZ and COBRA therapy on the HAQ score, but it remains likely that most of the HAQ scores did not represent irreversible disability but rather reflected reversible disability caused by disease activity.

We observed some interesting time trends with respect to the relationship between DMARD use and outcome. First, use of prednisolone in both groups was relatively rare compared with that reported in recent US studies of early RA. This is relevant with respect to long-term toxicity, because prednisolone could be tapered and withdrawn completely in the majority of patients. Second, use of MTX increased over time in both groups, while use of SSZ decreased, which suggests that SSZ was deficient in suppressing disease activity over time, and that MTX therapy was considered to be more efficacious. Apparently contradictory to these observations is the finding that during followup, MTX use, in contrast with SSZ use, was associated with *more* instead of less radiologic damage and with higher disease activity. This paradox is a typical example of confounding by indication, which in this case means that patients with more severe disease were more likely to switch to MTX. In other observational studies, prednisolone has been similarly associated with negative outcomes (23). We suggest that confounding by indication may also have been operative in those studies; as in our study, "correcting" for disease activity and other prognostic characteristics may not correct such a spurious association.

Our findings suggest 2 different concepts: 1) aggressive DMARD therapy works best very early in the course of RA, and 2) long-term associations between DMARD use and radiologic progression cannot be investigated in observational studies in which treatment allocation was not random but instead was based on patient-specific characteristics. The long-term effects of initial COBRA therapy on the rate of radiologic progression may well have been caused by a profound suppression of inflammation during the first year of treatment, which is reflected by a significantly lower time-averaged DAS28 at 1 year of observation. Subsequently, no "rebound" occurred in the COBRA group: the time-averaged DAS28 decreased slightly and slowly over time in both groups but at a higher rate in the SSZ group. Therefore, the between-group difference should disappear after ~7 years.

An important attribute of the COBRA scheme is the high oral pulse dosage of prednisolone, which is a profound suppressor of disease activity. It is possible that by suppressing disease activity to a very low level, the rate of radiologic progression can be reset.

Radiologic damage starts at the synovium–cartilage junction with invasion of fibroblast-like synovial cells. These aggressive cells proliferate under the influence of a proinflammatory cytokine milieu, possibly because they carry intrinsic genetic defects that prevent them from undergoing apoptosis. Angiogenic factors are generated that induce new blood vessels, which in turn feed the pannus tissue and help make the destructive events irreversible (for review, see ref. 24). High-dose prednisolone has been shown to suppress production of proinflammatory cytokines (25), to induce apoptosis (26), and to inhibit angiogenesis (27). Because of the progressive character of the pathophysiologic process that is the basis of radiologic damage, we believe that both the high initial dosage of prednisolone and its timing are crucial for achieving the effects seen in the COBRA group. A low maintenance prednisolone dosage (up to 10 mg/day) has also been shown to inhibit radiologic progression (28), but in this study progression resumed at 2 years, when prednisolone was stopped (29).

The importance of timing emanates from the observation that the degree of radiologic damage itself predicts the progression rate thereafter. Therefore, the best way to prevent further radiologic damage is to start therapy before such damage has occurred.

We have now shown that there is a window of opportunity of at least 12–24 months after the diagnosis within which aggressive therapy should start in order to limit radiologic progression over time. Within this window, disease duration was not a predictor of long-term radiologic progression. Recently, new treatment modalities have emerged, such as leflunomide (30) and tumor necrosis factor (TNF)–blocking agents (31,32), which effectively suppress disease activity and may retard or arrest radiologic progression, even if applied later in the course of the disease (31). We expect that any therapeutic approach that strongly suppresses disease activity during the window of opportunity will produce long-term effects such as those seen in our study. However, because data in patients with early RA are limited, and followup study of these drugs does not exceed 2 years, this hypothesis remains to be proven. In addition, high costs—especially of TNF-blocking agents—limit broad availability.

In summary, brief but intensive combination therapy that includes an oral pulse of corticosteroids (COBRA) early in the course of RA has effects that persist for many years. Compared with SSZ monotherapy, such an approach results in sustained suppres-

sion of the rate of radiologic progression, independent of subsequent DMARD use and disease activity.

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