

# Benefit of very early referral and very early therapy with disease-modifying anti-rheumatic drugs in patients with early rheumatoid arthritis

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**Objective.** Delay of disease-modifying anti-rheumatic drug (DMARD) therapy is a major contributing factor for poor outcome in rheumatoid arthritis (RA). Although early therapy has been shown to be particularly effective, there is still uncertainty about the optimal time point of DMARD introduction. We wanted to test if a therapeutic window of opportunity may exist within the first few months of the disease.

**Methods.** In this case-control parallel-group study, 20 very early RA (VERA) patients with median disease duration of 3 months were age and gender matched to a group of 20 late early RA (LERA) patients with median disease duration of 12 months until first DMARD initiation. Follow-up time was 36 months. Primary outcome measures were the disease activity score (DAS28) and radiological joint destruction using the Larsen method.

**Results.** Already after 3 months of DMARD therapy we found a significant difference of improvement in favour of the VERA patients in the DAS28. This trend continued over the study period. At study end the DAS28 showed an improvement of  $2.8 \pm 1.5$  in the VERA vs  $1.7 \pm 1.2$  in the LERA group ( $P_c < 0.05$ ). The Larsen scores showed a statistically significant retardation of progression in the VERA compared with the LERA.

**Conclusion.** Our results indicate that there is a window of opportunity for highly successful treatment of RA in the first year, and especially within the first 3 months of therapy. Thus, early diagnosis and therapy may be the crucial step in achieving optimal control of disease progression and prognosis in RA.

**KEY WORDS:** Very early rheumatoid arthritis, Disease-modifying anti-rheumatic drugs, Larsen score, DAS28, Therapeutic window.

Rheumatoid arthritis (RA) is an inflammatory rheumatic disease leading to joint destruction and loss of function and quality of life [1–3]. The cause of the disease is unknown, but immunological and inflammatory processes associated with subsequent destructive mechanisms appear to be already set off at the very beginning of RA [4, 5]. Therefore, it seems reasonable that therapeutic intervention should start very soon after disease onset, with the aim of stopping inflammation before irreversible damage is caused [6]. Therapy of RA rests mainly on the use of disease-modifying anti-rheumatic drugs (DMARDs) such as methotrexate (MTX), sulphasalazine (SSP) and leflunomide, which have been shown to retard disease progression, including joint destruction [7–10]. Recent pathogenic insights have led to the development and successful application of new biological therapies [11–15]. Despite these advances, remissions are rare and disease progresses in many patients.

Early application of DMARDs has revealed significant benefit when compared with their use later in the course of the disease [16–20], and in fact today most rheumatologists strongly recommend early introduction [21–25]. However, even early DMARD therapy does not fully prevent disease progression in the majority of the patients and, importantly, the term ‘early’ is still ill-defined: in clinical trials of ‘early RA’, patients with disease durations of a few months to 5 yr were included [17, 20, 26–30]. To date, though, there are no data actually comparing prospectively the outcome of

very early intervention with only briefly delayed DMARD therapy in patients with early RA.

In the present study we have tested to see if such a window of opportunity exists and thus compared, in a parallel study design, disease activity, joint destruction and functional outcome in patients with very early RA with those of age- and gender-matched patients who have experienced a short delay in disease-specific therapy.

## Patients and methods

### General study design

In this prospective, observer-blinded, parallel-group trial two groups of patients were compared; a power size calculation was performed and revealed that a study with 20 patients per group had a statistical power of 80% to detect a minimum of 35% difference in progression of primary endpoint measures [31, 32]. One group consisted of 20 consecutive individuals with very early rheumatoid arthritis (VERA1, as defined below), in whom DMARD therapy was started at a median of 3 months after the onset of symptoms. The control group consisted of 20 age- and gender-matched patients with late early rheumatoid arthritis (LERA, as defined below), in whom DMARDs were instituted at a median of 12 months after onset of symptoms.

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In this study we hypothesized that DMARD treatment introduced very early, as soon as only a few weeks after onset of symptoms, would be significantly superior when compared with a delay of DMARD initiation of only a few months, suggesting a therapeutic window of opportunity in this very early stage of the disease. For evaluation of efficacy, the core set of disease activity measures for RA clinical trials was used. Primary endpoints were defined as the difference in disease activity score and the change of radiological joint damage as assessed by the Larsen score.

The patient groups were followed during the same time period employing a similar therapeutic approach. Before inclusion of the first patient in 1997, a widely publicized 'Early Arthritis (EA) Action' was launched [33], leading to a significant increase in early referrals to our specialized units. All patients received routine patient care from rheumatologists who were unaware of the comparative purpose of the study. However, as a general policy, all physicians of the clinics are instructed to treat patients with DMARDs as early as possible, as aggressively as their disease state requires and as current practice dictates, and to switch DMARDs as soon as it is deemed clinically appropriate, i.e. if active disease persists after 3 months of DMARD therapy at effective doses, such as 3 g of SSP/day or  $\geq 15$  mg of MTX/week. The choice of DMARD was left to the rheumatologists' discretion. Neither the use of corticosteroids nor the use of NSAIDs was pre-defined.

For the two main patient cohorts, VERA1 and LERA, this study design balanced the treatment strategies, and allowed optimal investigation of real-life therapy with traditional DMARDs.

A final third group consisted of the next 20 consecutive VERA patients from the early arthritis clinic (VERA2). The additional VERA2 group allowed us to test the validity of data obtained in VERA1 patients.

This design seemed to be the appropriate way to address the clinically important question of the optimal time point of DMARD intervention, since a randomized trial of immediate versus delay of treatment for several months could be considered unethical on the basis of current clinical data.

The study has been approved by the Ethical Committee of the Vienna General Hospital and complies with the GCP guidelines according to the Declaration of Helsinki. A detailed design of the EA action has been reported previously [33]. All subjects gave written informed consent. Patients were assessed and managed at the rheumatological out-patient clinics of the General Hospital and the Lainz Hospital, both in Vienna, by a multidisciplinary team, including rheumatologists and a specialized occupational health therapist.

All patients were followed for a total of 3 yr. The date of DMARD start was defined as baseline.

#### *Very early rheumatoid arthritis—VERA1 patients*

The first 20 consecutive patients in the early arthritis clinic seen within 3 months from symptom onset and diagnosed as RA constituted the VERA1 cohort of patients. Since the American College of Rheumatology (ACR) classification criteria for RA [34] do not apply at the very early stage of the disease [33, 35–37], diagnosis of RA was made by the participating rheumatologists based on the clinical signs and symptoms and on laboratory tests, and ascertained by chart review after 1 yr. However, all patients fulfilled the ACR criteria at least at baseline and/or cumulatively during their first year of follow-up.

As soon as RA was diagnosed, patients were consequently treated with DMARDs. The date of DMARD start was defined as baseline.

#### *Late early rheumatoid arthritis—LERA-patients*

Each of the 20 VERA1 patients described above was matched to the first RA patient seen in clinic who matched by age ( $\pm 2$  yr) and gender, and who was presenting in clinics for the first time with a symptom duration between 9 months and 3.5 yr, and had never received DMARDs before (LERA). Diagnosis was made by the rheumatologists in charge, and, as in the VERA1, all patients fulfilled the ACR criteria already at baseline and/or during their first year of follow-up.

Again, patients were treated with DMARDs as soon as RA was diagnosed, and the date of DMARD start defined as baseline.

#### *'VERA2' patients*

In order to validate the data obtained from the VERA1 group, a second group of the next 20 consecutive very early arthritis patients (VERA2) was evaluated in the same way as VERA1 and LERA, but at a subsequent point in time.

#### *Clinical and laboratory investigations*

For evaluation of efficacy the core set of disease activity measures for RA clinical trials was used [38–40]. All variables were assessed prospectively.

The primary endpoints were the difference in disease activity score [42] and the change of radiological joint damage as assessed by the Larsen score [43], an established surrogate of outcome [38, 39, 44]. Secondary endpoints were differences in core set variables including function-related quality of life by Health Assessment Questionnaire (HAQ), as well as the ACR and the European League Against Rheumatism (EULAR) response rates [45, 46].

#### *Disease activity score (DAS28)*

The DAS28 [41, 42], a composite score calculated from joint counts (TJC, tender joint count; SCJ, swollen joint count), acute phase response (erythrocyte sedimentation rate, ESR) and patient global assessment (PGA) was evaluated as a measure of RA activity [ $\text{DAS28} = 0.56 \times (\sqrt{\text{TJC}}) + 0.28 \times (\sqrt{\text{SJC}}) + 0.70 \times \ln(\text{ESR}) + 0.014 \times \text{PGA}$ ]. A DAS28 score of  $\leq 3.2$  is defined as low activity,  $> 3.2$ – $5.1$  as moderate activity and  $> 5.1$  as high activity [42].

#### *Radiographic assessment*

Initial radiographs and radiographs at 12, 24 and 36 months, blinded for group and sequence, were assessed at the same time by a team of two experienced readers, one rheumatologist (KPM) and one radiologist (MU). In order to characterize precision of assessment, the complete sets of X-rays were reassessed at a different time point. Agreement between the assessments revealed a correlation coefficient of 0.86 [95% confidence interval (CI) 0.805 to 0.906].

Scoring was done according to the Larsen method on 42 joints in the hands/wrists and feet. Radiographs were compared with standard reference films and scored from 0 (normal) to 5 (mutilating changes) for each individual joint [43]. Accordingly, the possible range of the summary joint count score was 0–210. The number of eroded joints (defined by Larsen scores  $\geq 2$ ) was also calculated. Joint involvement was expressed as mean Larsen scores and by eroded joint counts.

### Functional assessment, pain and global assessment, joint counts, acute phase response and rheumatoid factor

Functional disability was assessed using the Stanford HAQ [47] in a validated German version [48].

Visual analogue scales (from 0 to 100 mm) were used for the evaluation of pain intensity and physicians' as well as patients' global assessment of disease activity.

Tender and swollen joint count scores were based on the 28 joint count [49, 50]. All joint counts were performed by an independent and blinded assessor.

Laboratory analyses according to standard techniques included the ESR and C-reactive protein (CRP) as measures of the acute phase response, and rheumatoid factor (RF) determined by nephelometry.

### ACR and EULAR response criteria

The ACR 20, 50 and 70% [45] and the EULAR response criteria composed of categorical changes in the DAS28 [46] are validated criteria for the assessment of treatment response [51]. Both scores emphasize change in disease state, and are therefore useful for assessing clinically relevant improvement in disease activity.

### Follow-up

For all groups follow-up data obtained at baseline, at 3 months and at yearly intervals thereafter will be shown, with the exception of radiographic assessment, which was assessed at yearly intervals only.

Our analyses of data at 1 yr after DMARD start are complete for all 40 VERA and LERA patients. During the second year two patients (one VERA1, one LERA) were lost to follow-up and another during the third year (one LERA). Two of these patients moved to other cities or countries and one was lost to follow-up because he did not return to our clinics and could not be accessed.

### Statistical analysis

Differences in the DAS28 and the Larsen score were employed as primary outcome variables. Changes from baseline values of individual core set variables (including HAQ) as well as the ACR 20, 50 and 70%, and the EULAR response rates served as secondary endpoints. Changes from baseline values are presented as mean values  $\pm$  standard deviation if not indicated otherwise.

Continuous variables were compared using the Wilcoxon signed rank test for paired data; binary variables were analysed using the McNemar test. To adjust for multiplicity, *P* values were corrected using the Bonferroni/Holm method in primary outcome variables (*P<sub>c</sub>*).

Missing observations for each of the lost to follow-up patients and the data of the complementary paired patient from this exclusion point on were carried forward until the end of the observation period (LOCF). As an exception, results of Larsen scores exclude matched patient pairs with any missing data at the respective point in time. At 1 yr, however, Larsen scores were available for all patients.

SPSS statistical software (SPSS Inc., Chicago, IL) was used for statistical analysis. The reported *P* values are the results of two-sided tests. A *P* (*P<sub>c</sub>*) value smaller than or equal to 5% was considered statistically significant.

## Results

### Demographics and baseline characteristics

Table 1 shows the baseline characteristics of the VERA and the LERA groups. The median disease duration (25th, 75th percentile)

TABLE 1. Demographic and baseline characteristics

	VERA1	LERA	VERA2
Number of patients	20	20	20
Mean age (yr)	54	53	54
Age range (yr)	25–78	25–80	25–79
Female (%)	75	75	85
RF positive (%)	45	40	45
With erosions (Larsen $\geq 2$ ) (%)	25	50	25
Median disease duration until DMARD start (25th, 75th percentile) (months)	3 (2, 4)	12 (9, 30)	3 (1.5, 4.5)
Previously taking DMARDs (%)	0	0	0
Receiving NSAIDs (%)	85	95	90
Receiving corticosteroids (%)	60	55	60

DMARDs, disease modifying anti-rheumatic drugs; RF, rheumatoid factor; NSAIDs, non-steroidal anti-inflammatory drugs.

from symptom onset until DMARD start in the VERA1 group was 3 (2, 4) months and that of the LERA group 12 (9, 30) months. VERA2 had the same characteristics as VERA1. Demographic variables, such as age, sex and RF status were very similar among the three groups. However, not surprisingly, while only 25% of the VERA patients had erosions at the start of DMARD therapy this was the case in 50% of the LERA patients. The number of patients receiving corticosteroids or non-steroidal anti-inflammatory drugs (NSAIDs) at baseline was comparable [*P* = not significant (n.s.)].

### VERA1 exceeds LERA in improvement of DAS28/EULAR response

The changes in mean DAS28 scores are shown in Fig. 1 (at 1 yr:  $-2.72$  in VERA1 and  $-1.61$  in LERA, *P<sub>c</sub>* < 0.05). An overall good response was obtained in the VERA1 but not in the LERA patients: at baseline mean DAS28 in both groups was in the high disease activity range (60% of the VERA1 patients and 50% of the LERA had a DAS28 > 5.1, *P<sub>c</sub>* = n.s.). Within 3 months of DMARD therapy the DAS28 decreased by about 40% compared with baseline in the VERA1, but by an insignificant 12% in the LERA group (*P<sub>c</sub>* < 0.05 between the two groups). After 1 yr, the mean DAS28 had even reached the low disease activity range among VERA1 patients, where it stabilized for the subsequent 2 yr. Such low mean disease activity was never achieved in the LERA group: a DAS28  $\leq 3.2$  was observed at 3 yr in 75% of the VERA1 but only 35% of the LERA patients (*P<sub>c</sub>* < 0.05 between the two groups). Moreover, a remission-like state (DAS28 < 2.6) was seen in 50% of VERA1 and 15% of LERA patients.

According to the EULAR response criteria, 16 of the VERA1 (80%) and 13 of the LERA patients (65%) were judged to be responders (good and moderate response, *P* = n.s.) after 3 yr of treatment. Eight of the VERA1, but only two of the LERA responders had a good response (*P* < 0.05). Thus, while EULAR response rates were not statistically different, the number of good responders among overall responders was four-fold higher in the VERA1 population.

### Retardation of radiographic damage is greater in the VERA than LERA group

At baseline, Larsen scores were  $3.5 \pm 4.4$  in the VERA1, and  $11.3 \pm 10.0$  in the LERA group (*P<sub>c</sub>* < 0.05). After 36 months of DMARD therapy, Larsen scores increased by  $3.6 \pm 6.5$  in the VERA1 and by  $14.7 \pm 9.9$  in the LERA group (Fig. 2). Changes from baseline were significantly higher (more than four-fold) in the LERA patients when compared with the VERA group (*P<sub>c</sub>* < 0.05). While five VERA1 and 10 LERA patients had erosions (Larsen score  $\geq 2$ ) at baseline (*P* < 0.05), the number of patients with

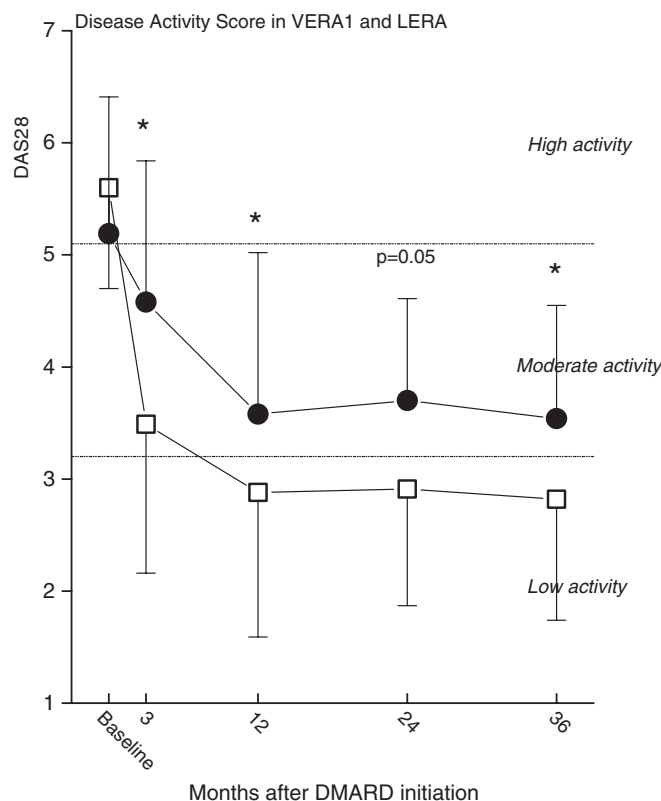


FIG. 1. Disease activity score (DAS28) in LERA (●) and VERA1 (□) patients at baseline and during the follow-up period. Baseline values were comparable, but already after 3 months decreased to a significantly lower level in the VERA1 group compared with the LERA group. Broken lines separate low, moderate and high activity levels of disease. Data presented as mean  $\pm$  s.d. \* $P_c < 0.05$  (Wilcoxon).

erosions at 36 months was seven in the VERA1 and 15 in the LERA group ( $P < 0.05$ ). Thus, in both groups the frequency of patients with erosions increased by about 50%, but among VERA1 the number of patients with erosions was even lower at 3 yr than among LERA at baseline.

The biggest increase of the Larsen score was seen in the LERA group within the first year (scores of first year vs second year,  $P_c < 0.05$ ). Interestingly, after 36 months of DMARD therapy (median disease duration 39 months from onset) Larsen scores of VERA1 patients had not reached even the baseline Larsen scores of LERA patients ( $P_c < 0.05$ ). Moreover, the most prominent increase in Larsen scores was seen during the first year among LERA, while the radiographic progression in LERA paralleled that seen in VERA1 thereafter. In contrast, the slope of the radiographic progression in VERA1 was linear throughout the observation period.

#### *Changes in functional outcome, but not joint counts or acute phase response, are more pronounced among VERA than LERA patients*

The changes from baseline in variables assessed at 3 months and at the study endpoint at 36 months are shown in Table 2. As soon as 3 months after DMARD start in both groups, there was a significant difference in favour of the VERA1 group with respect to the disability score (HAQ), and this significant difference was maintained through year three. Thus, while both groups started with a

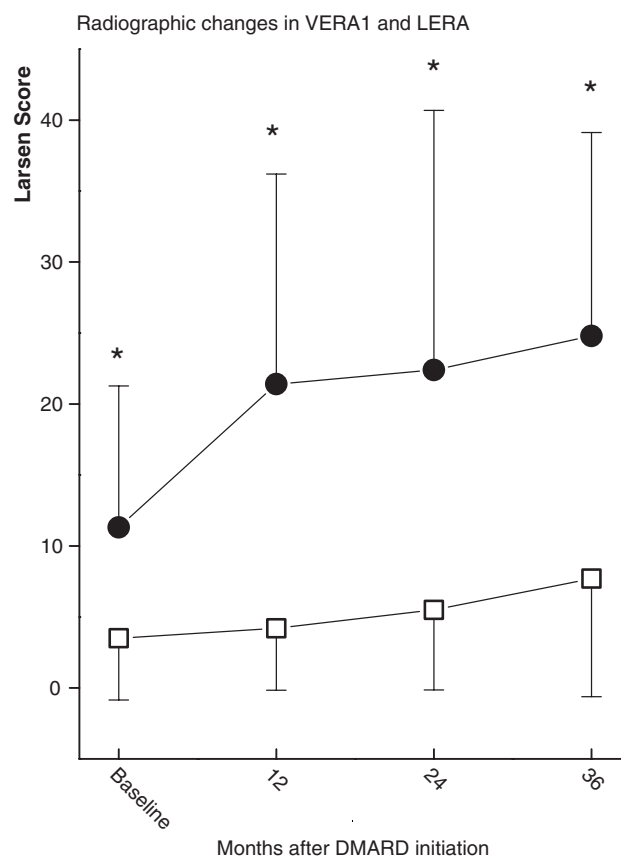


FIG. 2. Radiographic changes in LERA (●) and VERA1 (□) patients, indicated by the Larsen score at baseline and after 12, 24 and 36 months of follow-up. A parallel slope of both groups with a significantly higher level of joint destruction was observed in the LERA group from the 1 yr follow-up point on. Data presented as mean  $\pm$  s.d. \* $P_c < 0.05$  (Wilcoxon).

similar disability score (0.9), this score was 150% higher in the LERA group (0.5) than in the VERA1 group (0.2) after 3 yr.

A similar development can be seen for pain assessment and both the physicians' as well as the patients' global assessments, with significant differences between VERA1 and LERA. In contrast, although numerically favouring VERA1, changes in joint counts were statistically different only for tender joint counts at the 3-yr time point.

The development of the acute phase response as measured by ESR and CRP is shown in Table 3. A decrease was demonstrated for both variables in both groups after only 3 months of DMARD therapy with continuing reduction until study end, when both the mean ESR and CRP values were quite close to their normal range, with no significant difference between the two groups.

#### *ACR response criteria favour very early therapy*

When ACR 20, 50 and 70% responses were analysed, VERA1 patients again had significantly higher improvement rates than LERA patients (Fig. 3): after 3 months 65% of the VERA1 as opposed to 20% of the LERA patients had achieved an ACR 20% response ( $P < 0.05$ ), 50% VERA1 vs 15% LERA an ACR 50% response ( $P < 0.05$ ) and 35% of VERA1 fulfilled an ACR 70% response whereas none of the LERA did ( $P < 0.05$ ).

After 36 months 70% of the VERA1 vs 40% of the LERA patients fulfilled the ACR 20% response criteria ( $0.1 > P > 0.05$ ), 60% of VERA1 vs 25% of LERA patients a 50% ( $P < 0.05$ ) and 55% vs 20% an ACR 70% response, respectively ( $P < 0.05$ ).



TABLE 2. Changes in clinical core set variables

		VERA1	LERA	P
HAQ score (0–3)	Baseline	0.9 (0.8)	0.9 (0.6)	n.s.
	Change at 3 months	–0.5 (0.8) (–56%)	–0.1 (0.3) (–11%)	<0.05
	Change at 36 months	–0.7 (0.7) (–78%)	–0.4 (0.6) (–44%)	<0.05
Patients' pain assessment (VAS, mm)	Baseline	52.0 (17.4)	50.0 (16.9)	n.s.
	Change at 3 months	–29.3 (31.2) (–56%)	–7.2 (22.0) (–14%)	<0.05
	Change at 36 months	–40.4 (21.7) (–78%)	–24.9 (24.3) (–50%)	<0.05
Patients' global assessment (VAS, mm)	Baseline	46.5 (19.4)	50.1 (18.5)	n.s.
	Change at 3 months	–22.3 (33.0) (–48%)	–6.7 (21.3) (–13%)	<0.05
	Change at 36 months	–35.8 (21.9) (–77%)	–24.2 (24.4) (–48%)	<0.05
Physicians' global assessment (VAS, mm)	Baseline	48.4 (20.4)	41.7 (15.0)	n.s.
	Change at 3 months	–30.5 (26.0) (–63%)	–6.6 (19.5) (–16%)	<0.05
	Change at 36 months	–38.0 (24.2) (–79%)	–19.5 (23.5) (–47%)	<0.05
Swollen joint count	Baseline	9.1 (6.8)	7.2 (5.1)	n.s.
	Change at 3 months	–6.6 (7.2) (–73%)	–2.9 (4.3) (–40%)	n.s.
	Change at 36 months	–7.5 (7.8) (–82%)	–4.8 (5.0) (–67%)	n.s.
Tender joint count	Baseline	9.7 (7.8)	7.1 (6.8)	n.s.
	Change at 3 months	–6.8 (8.2) (–70%)	–1.9 (5.4) (–27%)	n.s.
	Change at 36 months	–8.0 (8.6) (–82%)	–4.5 (7.1) (–63%)	<0.05

HAQ, Health Assessment Questionnaire; VAS, visual analogue scale; n.s., not significant.

Data presented as mean (s.d.) and percentage change from baseline (%) comparing results between groups.

P values for VERA1 vs LERA.

TABLE 3. Acute phase response

		VERA1	LERA	P
ESR (mm/h)	Baseline	49 (28; 69)	38 (20; 63)	
	At 3 months	22 (14; 31)	25 (17; 48)	n.s.
	At 36 months	19 (10; 25)	18 (16; 38)	n.s.
CRP (mg/l)	Baseline	28.0 (9; 40)	18.1 (11; 31)	
	At 3 months	7.6 (5; 15)	10.3 (6; 22)	n.s.
	At 36 months	5.1 (5; 10)	7.9 (5; 16)	n.s.

Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) for the VERA1 and LERA group. Normal ranges for ESR <20 mm/h and CRP <5 mg/l. n.s., not significant.

Data presented as median (25th; 75th percentile).

ACR Response in VERA1 and LERA

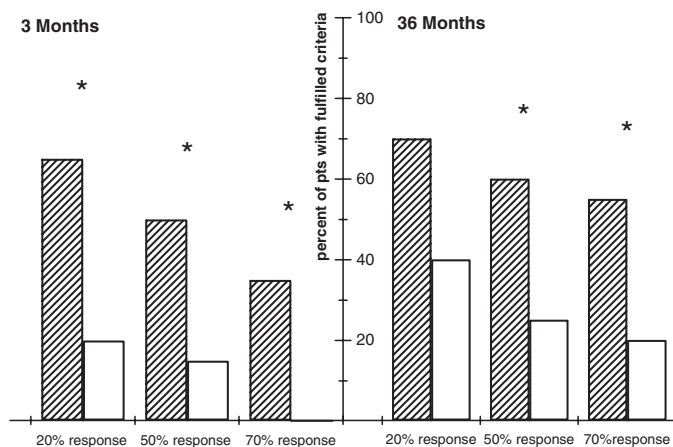


FIG. 3. Per cent of patients fulfilling ACR response criteria after 3 (left panel) and 36 months (right panel) of follow-up. More patients in the VERA1 group (hatched columns) reached the ACR criteria at both time points than in the LERA group (white columns). \* $P < 0.05$  (McNemar).

#### Patients lost to follow-up

A total of three patients were lost to follow-up during the 3-yr period of observation: one VERA and two LERA patients. Data

for each of these patients plus their matched control were interpreted using the LOCF method but fully excluded for radiological analysis. We calculated all our data with the 17 complete pairs that continued treatment over 36 months (not shown). The results were very similar to the ones shown.

#### Switches of DMARD therapy due to lack of efficacy are common among LERA

The evolution of DMARD usage over time reflected the clinical data. The initial distribution of DMARDs was similar when the two groups were compared (Table 4). However, DMARDs of four VERA1 patients were subsequently switched once, and twice or three times in each one additional patient (the total number of regimen changes was nine). In contrast, among LERA patients, switching of DMARDs was necessary once in six patients, twice in two and three times in one patient (total changes 13). Interestingly, of the nine switches in the VERA1 group, six were due to adverse events and three due to inefficacy, while in the LERA group four switches were due to adverse events and nine due to inefficacy. Thus, DMARD switching due to lack of efficacy were three-fold ( $P < 0.05$ ) more frequent among LERA than VERA1 patients.

#### VERA1 and VERA2 are similar

Demographics of the VERA2 group are shown in Table 1. The distribution of DMARDs was similar to those used in the VERA1 group (SSP,  $n = 8$ ; MTX,  $n = 7$ ; chloroquine (CQ),  $n = 4$ ; CQ + MTX,  $n = 1$ , at baseline). In Fig. 4 DAS28 scores over time are shown for VERA1 and VERA2 (upper panel). The scores of both groups were almost identical throughout the period of observation. Fig. 4 also shows the Larsen scores (lower panel) of VERA1 and VERA2: as for the DAS28, the increase in mean Larsen scores was almost the same over the 3-yr observation period. Moreover, when the DAS28 and Larsen scores of the VERA2 patients were compared with those of LERA patients, the differences between these two groups were similar to those obtained for the VERA1 cohort versus the LERA patients (data not shown).

TABLE 4. DMARD therapies

DMARD	At baseline = DMARD start				At 3 yr			
	VERA1 (n = 20)	Dose <sup>a</sup> (median, mg)	LERA (n = 20)	Dose (median, mg)	VERA1 (n = 19)	Dose (median, mg)	LERA (n = 18)	Dose (median, mg)
SSP	9	2000	8	2000	6	2000	4	2500
MTX	5	7.5	8	7.5	8	15	6	20
CQ	5	250	4	250	4	250	2	250
CQ + MTX	1	250 + 12.5			1	250 + 10	1	250 + 25
CyA + MTX							1	200 + 20
SSP + MTX							1	3000 + 15
Leflunomide							3	20

DMARD, disease-modifying antirheumatic drugs; SSP, sulphasalazine; MTX, methotrexate; CQ, chloroquine; CyA, cyclosporin A.

<sup>a</sup>At 1 month from DMARD start.

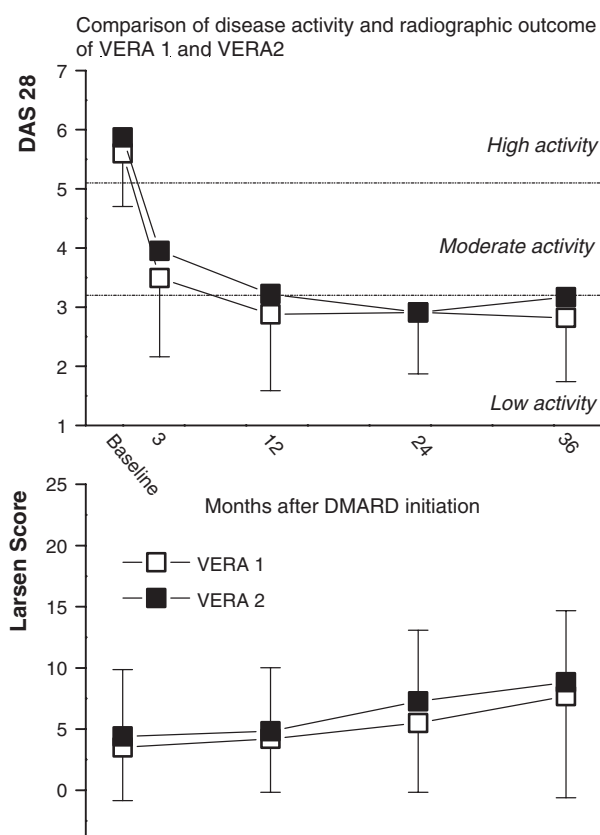


FIG. 4. Disease activity score (DAS28, upper panel) and Larsen score (lower panel) in the VERA1 (□) and VERA2 (■) group. No significant differences were observed between groups at baseline or during follow-up ( $P = \text{n.s.}$ ). Data presented as mean  $\pm$  S.D.

## Discussion

It has been recognized for several years that early DMARD therapy confers a significant therapeutic advantage in rheumatoid arthritis, in particular when compared with more conservative therapeutic approaches [52]. However, when relating to a chronic disease that afflicts its victims for many decades, the term 'early' is difficult to define, and hence clinical trials in early RA have included patients with disease duration of 1 and up to 5 yr [16, 17, 20, 26–30]. The results of these trials suggested that the value of early DMARD therapy lies in improved outcome related to function, quality of life and joint destruction.

To establish whether there exists a window of opportunity within early disease, we formed two groups: one group of patients with very early RA, with a median of 3 months' symptom duration before DMARD start, and a fully matched group of patients with late early RA, with a median symptom duration of 12 months, who would still have qualified for most previously published early RA trials.

The results obtained show that throughout the period of observation, and despite similar therapies, there were significant differences in disease activity, joint destruction and functional outcome in favour of very early therapy. Most importantly, the major differences between the two groups occurred within the first year and especially during the first 3 months of treatment. This was particularly true for functional disability, disease activity and radiographic progression of joint destruction.

This suggests that in very early arthritis, but not in arthritis lasting for just a short time longer, disease progression can be halted rapidly. Moreover, these therapy-driven data confirm epidemiological indications that arthritis of more than 12–24 weeks' duration will cause increasing damage [53, 54].

The data also suggest that, when treated very early, a large fraction of patients respond very well to traditional DMARDs (ACR 50% response in 60% of patients after 36 months), allowing levels of effectiveness to be achieved that approach or even exceed those obtained with the best recently introduced agents, including biological therapies, which were not licensed in Europe until almost the end of the inclusion period. These latter costly therapies could then be reserved for those patients who do not respond well to traditional approaches, and still be used relatively early for the benefit of the patients.

Could the excellent therapeutic results obtained among VERA1 patients have been due to spontaneous remissions or 'contamination' of this group with non-RA patients? This is highly unlikely for several reasons: Firstly, with one exception, VERA1 patients had persistent arthritis for more than 6 weeks and 70% for at least 3 months, important time points for the differentiation between early RA and early non-RA [34, 53, 54]. Secondly, a good DAS28 response was not observed more frequently among VERA1 patients with  $\leq 3$  compared to those with  $> 3$  months' disease duration at DMARD start (data not shown). Thirdly, RF status was similar in both groups, and numerically even higher among VERA1 patients, and corresponds well to other early RA cohorts [19]. Fourthly, the frequencies of patients with erosive disease increased by around 50% during the 3 yr of observation in both groups, further supporting the diagnosis of RA. Also, for both VERA and LERA patients, respectively, the data on joint damage at study start were similar to those published on investigations of similar cohorts of patients [17, 19, 20, 27, 53]. Finally, we could easily control for the results observed in the initial VERA1 group by assessing a second cohort of VERA2 patients: the differences

between LERA and VERA1 were fully confirmed when the LERA group was compared with the VERA2 cohort.

All patients were referred to our clinics in the context of a widely publicized Early Arthritis Action [33]. At the time of study onset, we had set inclusion criteria for the VERA and the LERA group. The LERA was defined, similar to those of other trials on 'early RA', as patients with maximum symptom duration of 3 yr [17, 28, 29]. When we evaluated the data retrospectively to include only patients with symptom duration of less than 1 yr and compared those LERA with their matching VERA1 equivalent, results (not shown) did not differ significantly from those observed for the total group.

This study did not constitute a randomized controlled therapeutic trial but a real-life design. However, assessment was performed in a blinded manner by independent observers. There was no selection bias regarding the VERA group, since consecutive patients were included. The treating physicians were unaware of the comparative purpose of the study, and different from the evaluators. They were only required to treat all RA patients in the clinic according to the state of the art, and, in fact, VERA and LERA patients were initially treated in a similar fashion, while their worse clinical course forced a more frequent and more rapid change of DMARD regime in LERA compared to VERA patients.

Thus, the data obtained suggest that, compared with very early RA, it is more difficult to control RA ongoing for a prolonged time, even if this 'prolonged' period is relatively short, i.e. a few months. This conclusion is supported by recent observations that first DMARD courses are particularly effective and more so than later DMARD courses [55, 56]. The data shown here suggest that the higher efficacy of first DMARD courses may be associated with their institution earlier in the disease course rather than with their earlier numerical sequence. Thus, our observations provide evidence that there exists a critical therapeutic window very early in the course of RA.

Interestingly, the surrogates of inflammatory disease activity did not differ between VERA and LERA patients: the acute phase response and joint swelling improved significantly in both groups of patients compared with baseline, but the changes observed in the VERA group were not significantly different from those of LERA patients at any point in time. Thus, although there exists a relationship between joint swelling and acute phase response on the one hand and radiographic damage on the other hand [57–59], the lack of difference regarding the inflammatory variables compared with the highly significant difference in structural changes support the notion of a dissociation of inflammation and destruction as recently evidenced in experimental models of arthritis [60, 61]; this dissociation appears to be particularly present in very early disease when inflammation is active but cartilage and bone structures have not yet been fully attacked. Thus, the data suggest that, although inflammation may be halted to a similar degree in very early and later RA, destruction, once initiated and progressing, is partly 'autonomous'. On the other hand, once disease was under control with DMARDs, i.e. after the first year, radiographic progression in later disease paralleled that in very early disease, suggesting that rapid reduction of inflammation is key also in established RA.

On the basis of publications on the efficacy of early DMARD therapy [16, 17, 19, 23–25, 62], rheumatologists are now alerted to start DMARDs as early as possible. Nevertheless, many physicians even today still prefer to wait for a few months before institution of DMARDs [63, 64]. Moreover, patients are often referred late after onset of symptoms [63]. In fact, the delay of DMARD start among LERA patients in our study was solely due to late referral.

The present data extend all previous notions on the importance of early DMARD therapy and reveal that 'early' cannot be early enough. Of course, as shown here, DMARDs can be highly

effective even in later stages of RA; however, even when DMARD therapy is only briefly delayed, RA patients may never catch up for the loss of time in terms of destruction and function.

In conclusion, based on the data presented, the major tasks for the immediate future will be to alert physicians that early referral may be the most important 'joint protecting' measure for patients with rheumatoid arthritis and that DMARD therapy should be instituted as early as possible, ideally within the first 3 months from onset of symptoms.

Rheumatology	Key messages
	<ul style="list-style-type: none"> <li>The study extends all previous notions on the importance of early DMARD therapy in RA by revealing the existence of a therapeutic window of opportunity within the first few months of the disease.</li> </ul>

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