Very Recent Onset Arthritis — Clinical, Laboratory, and Radiological Findings During the First Year of Disease

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ABSTRACT. ***Objective.*** To describe clinical and radiological findings in patients with very early arthritis (< 3 months of symptoms) during one year of observation.

Methods. In an Austrian multicenter setting, patients were eligible if they had nontraumatic swelling or pain in at least one joint and laboratory signs of inflammation [elevated erythrocyte sedimentation rate, C-reactive protein, leukocytosis, or rheumatoid factor (RF)] within the last 3 months. Clinical and laboratory assessments were performed every 3 months. Radiographs of hands and feet were taken at entry and after one year. Treatment decisions were left to the discretion of the participating center.

Results. In total, 108 patients included between 1996 and 2000 had followup investigations during at least one year; 61.1% of these patients had rheumatoid arthritis (RA). Over 65% of RA diagnoses were made at the first visit. Lag time to referral was significantly longer in patients with RA than in patients with other inflammatory joint diseases (median 8 vs 4 weeks). Disease modifying antirheumatic drugs were started 19 ± 10 (mean ± SD) weeks after symptom onset in patients with RA. Patients with RA improved significantly (by American College of Rheumatology response criteria and the Disease Activity Score 28) during the first year. Erosions were present in 12.8% of RA patients' initial radiographs, compared to 27.6% after one year. Odds ratio to develop new erosions during the first year of RA was 9.7 (95% CI 1.05–89.93) in RF+ patients compared to RF– individuals ($p < 0.05$).

Conclusion. When early referral of patients with arthritis is encouraged, RA can be diagnosed and treatment initiated early, with significant clinical response. Moreover, patients with RA tend to be referred later than patients with other inflammatory joint diseases; RA patients at this very early stage have low frequency of joint damage; and RF predicts erosions in the first year. (J Rheumatol 2002;29:2278–87)

Key Indexing Terms:
EARLY RHEUMATOID ARTHRITIS
PROGNOSIS
TREATMENT
FOLLOWUP

Treatment of rheumatoid arthritis (RA) aims at halting or at least retarding the complex destructive processes that are the hallmark of this most common inflammatory joint disease. The histological changes leading to the destruction of cartilage and bone are already present in very early stages of the disease[1] and in clinically involved as well as uninvolved joints[2].

To prevent joint destruction, disease modifying antirheumatic drugs (DMARD) such as methotrexate (MTX), antimalarials, gold salts, sulfasalazine, and, more recently, leflunomide and tumor necrosis factor blocking agents are employed. These drugs have been shown to control inflammation and retard destruction[3-13], although their effects on disability are much less well documented[14-16]. Since the destructive process can be quite rapid and detectable on radiographs after only a few months[17-19], early initiation of therapy has been regarded to be important[20].

There are, however, severe limitations to this seemingly straightforward concept. First, the disease may frequently present with an "atypical" onset, and, in early stages, may be indistinguishable from other arthritic conditions[21]. Second, even in well classified RA, the extent and course of the destructive changes are unpredictable and may be quite variable[22,23]; significant radiographic changes can already be seen within 6 months after diagnosis of the disease[19,24] or

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during a period of only 6 months of ineffective treatment[13]. Third, patients are rarely referred to the rheumatologist in early stages of the disease[25,26]. All these factors contribute to considerable delays in initiating effective treatment and may allow irreversible changes to occur, and consequently may pave the path to premature disability.

Thus, an important step toward improving the outcome of RA may lie in shortening the period between onset of symptoms and initiation of therapy. To this end, a number of rheumatological centers have initiated efforts to diagnose and treat patients early in the course of RA in so-called early arthritis clinics (EAC). However, the term "early" is currently still ill defined, and thus studies on "early RA" have analyzed patients who may have had symptoms for many months or up to several years[9,20,22,27-34].

We investigated patients of a very early arthritis clinic (VEAC) that allowed entry only for patients with less than 3 months' duration of symptoms[35]. It was our aim to study the features of very early RA in comparison to other arthritides in their earliest periods. Further, we describe the subsequent evolution of very recent onset RA clinically and radiologically.

MATERIALS AND METHODS

The "Early Arthritis Action" (EAA). Details of the EAA have been published[35]. Patients were enrolled in several Austrian rheumatology centers that participated in the study (Acknowledgment). "Early arthritis" was defined as any inflammatory joint disease of ≤ 3 months' duration from onset of symptoms. Inflammatory joint disease was defined as (1) swelling or pain not related to trauma in at least one joint, in addition to (2) laboratory signs of inflammation such as elevated erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) or leukocytosis (values above the upper limit of normal) or a positive test for rheumatoid factor (RF). The diagnosis of RA was given if patients fulfilled American College of Rheumatology (ACR) criteria for RA and had no exclusion criteria[36,37], or clinical examination revealed polyarthritis of ≥ 6 weeks' duration without evidence of other inflammatory rheumatic diseases upon investigation. (Since the 1987 ACR criteria have only been validated in established RA, we employed the 1958 exclusion criteria as well, in order to explicitly exclude other disorders with clinical features similar to RA.) In cases in which the diagnosis could not be ascertained by the caring rheumatologist, the disease was classified as undifferentiated arthritis. All diagnoses were reviewed by one of the authors (KPM). In cases where the data on the questionnaires did not unequivocally support the diagnosis given by the submitting center, the physicians at the center were asked to verify the correct diagnosis.

Questionnaires (a modified version of a published protocol[38]) with all pertinent questions on history, clinical findings, and laboratory investigations as well as on therapy (current and past) and its efficiency were distributed to rheumatology centers willing to participate in the initiative. After the initial visit, patients were planned to be seen at least every 3 months. At these quarterly visits the respective questionnaires were completed by the rheumatologists and the patients. In all patients, clinical and laboratory examinations were performed including joint counts (for swelling and tenderness) comprising the 28 joint count[39,40] plus ankles and the metatarsophalangeal (MTP) joints as a group (total of 32 joints). In addition, a validated Austrian version of the Health Assessment Questionnaire (HAQ)[41] was completed by the patients initially and at every quarterly visit.

Laboratory investigations were performed at every quarterly visit; they included complete blood counts, acute phase reactants (ESR and CRP), RF, and blood chemistry panel. In addition, a fluorescent antinuclear antibody test was performed at the initial visit. When deemed necessary, patients underwent detailed serologic and/or bacteriologic evaluation for reactive arthritis[42] or viral arthritis. The results of these tests were also recorded.

The completed questionnaires were mailed by the participating rheumatology clinics to the main centers of the EAA and entered into a database for analysis.

Radiographs. Routine radiographic imaging of hands and forefeet and, if present, other involved joints was planned to be performed at the time of entry into the study and yearly (± 3 mo) thereafter. Hands and forefeet were examined in the dorsovolar/dorsoplantar and oblique views. Radiographs were assessed according to the Larsen score[43]. In addition, for further analysis the numbers of patients with joint erosions were determined. For this report, radiographs were read by 2 radiologists and 2 rheumatologists experienced in the assessment of joint radiographs. Reading sessions were held with all readers present. Disagreements in assessments were resolved immediately by consensus. The readers were blinded to the identity and diagnoses of the patients and scored serial radiographs (baseline and one year) at the same time, but blinded to the sequence. To characterize precision of assessment, 35 of the 63 complete sets of radiographs were reassessed at a different time. Agreement between the assessments was found to be good, with a correlation coefficient of 0.86 (95% CI 0.805–0.906).

Data analysis. Data derived from the questionnaires were entered into a computerized data file and analyzed using SPSS (v. 9.01, 1999) and GraphPad (v. 3.0, 1999) software. For nonparametric comparisons, chi-square and Fisher's exact test were employed, continuous data were analyzed using t tests (where appropriate) and Mann-Whitney U tests (for non-normally distributed variables).

RESULTS

Patients. Between 1996 and 2000, questionnaires for 219 patients were completed by the participating centers. At the end of 2000, 108 patients had been followed for at least one year. These patients constitute the focus of this report. Among the 111 patients for whom no complete one year followup was available, 59 were only seen once in one of the clinics and did not return for followup. The remaining 52 patients either had less than one year of observation at the time of census or had followup examinations during the first few months but did not return thereafter, so that one year data could not be evaluated. Only 3 centers, all located in Vienna, enrolled more than 10 patients.

Diagnoses. Basic demographic data on the 108 patients are shown in Table 1. RA was the most frequent diagnosis; RA was diagnosed in 66 individuals (61.1%) at some time during the observation period. Clinical and radiological findings in this group will be described in detail below. Forty-two patients (38.9%) had a diagnosis other than RA. The diagnoses (grouped in categories) are listed in Table 1A. The initial judgments of the rheumatologists, i.e., the tentative diagnoses of the patients, were confirmed during the one year followup in 70.4%; in 29.6% the tentative diagnosis had to be changed during Year 1 (Table 1B).

Time to diagnosis. In 45 (68%) of the 66 patients with RA followed for at least one year the tentative diagnosis (Figure 1) proved correct during followup; the initial provisional diagnoses in the 21 patients in whom RA was diagnosed at visit 2 or later were: polymyalgia rheumatica (n = 2), reac-

Table 1a. Demographics and final diagnoses (confirmed after one year) of the patients.

	Male	Female	All
n	27	81	108
RA	14	52	66
Non-RA	13	29	42
Age, yrs, mean ± SD			
All patients	58.9 ± 15.5	53.2 ± 17.5	54.6 ± 17.2
RA	64.6 ± 11.4	55.75 ± 16.5	57.6 ± 16.0
Non-RA	50.8 ± 17.0	49.3 ± 18.4	49.8 ± 18.0
Diagnosis by category			
RA	14	52	66
Reactive arthritis	6	8	14
Undifferentiated arthritis	4	12	16
Other arthritides*	3	8	11
Osteoarthritis	0	1	1

* Psoriatic arthritis (n = 4), systemic autoimmune diseases (lupus, polymyositis: n = 3), sarcoidosis/Löfgren's syndrome (n = 1), palindromic rheumatism (n = 2), arthritis with Crohn's disease (n = 1).

Table 1b. Change of diagnoses in patients with early arthritis followed ≥ one year. In 76 patients (70.4%), diagnoses obtained at the first visit were confirmed during followup; in 32 patients (29.6%), the initial diagnosis had to be revised within the first year.

Initial Judgment (tentative diagnosis)	Diagnosis After 1 Year	No. of Patients
RA	RA	45
RA	Undifferentiated arthritis	4
RA	Polymyositis	1
Reactive arthritis	Reactive arthritis	13
Reactive arthritis	RA	2
Reactive arthritis	Psoriatic arthritis	1
Reactive arthritis	Palindromic rheumatism	1
Reactive arthritis	Arthritis with Crohn's disease	1
Undifferentiated arthritis	Undifferentiated arthritis	12
Undifferentiated arthritis	RA	17
Undifferentiated arthritis	Reactive arthritis	1
Undifferentiated arthritis	Palindromic rheumatism	1
Osteoarthritis	Osteoarthritis	1
Psoriatic arthritis	Psoriatic arthritis	3
Polymyalgia rheumatica	RA	2
SLE	SLE	1
Polymyositis	Polymyositis	1
Neuropathic arthritis	Sarcoidosis	1
Total		108

tive arthritis (n = 2), and undifferentiated arthritis (n = 17). In 5 patients followed for more than one year, a provisional diagnosis of RA at their first visit was later revised to undifferentiated (oligo)arthritis (4 patients) and to polymyositis (one patient).

In the non-RA patients, the tentative diagnoses at the first visit turned out to be correct in 31 of 42 patients (74%). Thus, correct diagnoses were made by the rheumatologist at the first visit in over 70% of all patients with early arthritis.

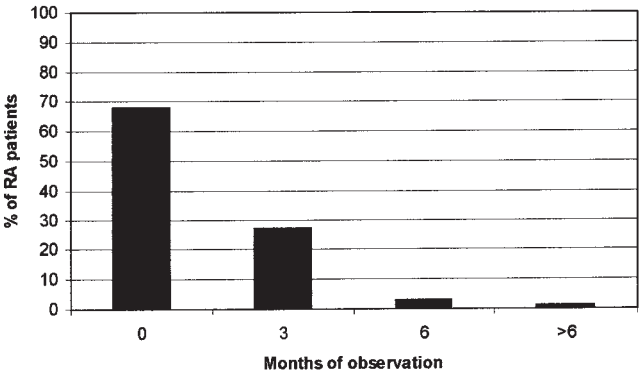

Figure 1. Time to diagnosis of RA: 45 of 66 patients followed for over one year were given the diagnosis at the first visit (i.e., less than 3 months after onset of symptoms), 18 were diagnosed 3–6 months after onset, and 3 were diagnosed 6–9 months after onset. In 2 individuals an initial diagnosis of seronegative (undifferentiated) oligoarthritis was changed to RA after more than one year.

Lag time of referral and acuteness of onset. One of the major aims of the EAA was to shorten the lag time from onset of symptoms to diagnosis of inflammatory rheumatic disease. Therefore, the duration of symptoms at the first visit was recorded for every patient. Data for 96 of the 108 patients were available for analysis: the 39 patients classified as "non-RA" after one year had a significantly shorter median symptom duration of 4 weeks [interquartile range (IQR) 2 to 8 weeks] at entry as compared to the 62 patients classified as RA after one year (median 8 weeks, IQR 4 to 10 weeks; $p < 0.01$ by Mann-Whitney test).

One item of the questionnaire at the first visit concerned the patients' rating of acuteness of the onset of their arthritis. A significantly higher proportion of patients in the non-RA group (57%) rated the onset of their arthritis as acute compared to the RA patients (40%; $p < 0.01$, chi-square test). This may, at least in part, explain their earlier referral.

ACR classification criteria. ACR classification criteria for RA were evaluated for their usefulness in the differentiation of RA from other disorders at first presentation to a rheumatologist. In accord with the results of other authors[44], the criteria were not very sensitive: in the group of the 66 patients with RA, a mean ± SD of 3.4 ± 1.2 ACR criteria were present at the first visit; 34 patients (52%) with RA fulfilled 4 or more criteria, but 32 patients initially presented with less than 4 ACR criteria for RA (Figure 2).

In the group of 42 non-RA patients, a mean of 1.9 ± 1.5 ACR criteria were fulfilled at visit 1; 34 patients in this group had less than 4 criteria present at the first visit, but 8 (19%) would have fulfilled the ACR criteria for RA at visit 1 (Figure 1). The diagnoses of the 8 non-RA patients with at least 4 criteria for RA were undifferentiated arthritis (4 patients), reactive arthritis (2 patients), systemic lupus erythematosus (SLE), and polymyositis (one patient each).

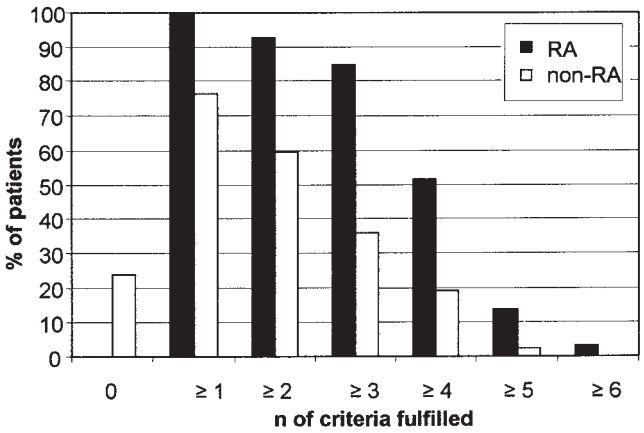

Figure 2. ACR criteria at visit 1. The percentage of RA patients fulfilling ≥ 4 ACR criteria for RA (52%) was significantly higher at visit 1 compared to the non-RA patients ($p < 0.0001$). Nevertheless, a considerable percentage of patients with RA did not fulfil ACR criteria initially, while several non-RA patients had ≥ 4 criteria. Numbers (percentages) of patients who fulfilled n criteria were as follows: n = 0: RA: 0 (0.0), non-RA: 10 (23.8); n = 1: RA: 5 (7.6), non-RA: 7 (16.7); n = 2: RA: 5 (7.6), non-RA: 10 (23.8); n = 3: RA: 22 (33.3), non-RA: 7 (16.7); n = 4: RA: 25 (37.9), non-RA: 7 (16.7); n = 5: RA: 7 (10.6), non-RA: 1 (2.4); n = 6: RA: 2 (3.0), non-RA: 0 (0.0).

Among the 66 RA patients there were 51 who fulfilled ACR criteria for RA at some time during the first year: 34 at the initial visit; 4, 3, and 2 patients fulfilled at least 4 criteria at the visits after 3, 9, and 12 months, respectively. Eight individuals fulfilled ACR criteria "cumulatively" (i.e., presence of several criteria at different time points) only. The 15 "ACR negative" RA patients were mostly seronegative (14 patients); all had polyarthritis of the hands and only 2 individuals had less than 3 criteria over time.

Rheumatoid factor (RF) and acute phase reactants. At the first visit, RF was detected in 36 of the 108 patients (33.3%). Among the 66 RA patients, 31 (46.9%) had a positive test for RF at the first visit. Two of those 31 patients had a negative result at the initial visit and became positive thereafter. The other patients had consistent (positive or negative) RF results throughout the observation period.

Among the 42 non-RA patients, 5 patients (11.9%) were RF positive: one patient each had palindromic rheumatism, polymyositis, and reactive arthritis, and 2 patients had arthritis classified as undifferentiated oligoarthritis.

The median initial CRP in the cohort of 108 individuals was 28.7 mg/l (IQR 9.1 to 61.7). Median ESR was 56 mm/h (IQR 25 to 79). At the baseline visit, CRP was normal in 15 (13.9%) of the 108 patients; ESR was < 20 mm/h in 19 (17.6%) patients. Both ESR and CRP were within the normal range in 6 individuals (5.6%). All these patients (3 with RA, 3 non-RA) had either documented elevated acute phase reactants at the time of referral (4 patients) or were RF positive at entry (2 patients). CRP and ESR values did not differ significantly between RA and non-RA patients (data not shown).

Joint counts and disease activity. At every visit, the number of swollen and painful joints (32 joint count) was recorded. Not surprisingly, at the initial visit, the number of painful and swollen joints in the RA patients was higher than in the non-RA patients (Table 2). In contrast, visual analog scales (VAS) for pain and disease activity as judged by patients and VAS for disease activity assessed by the physicians were not significantly different between the RA and the non-RA patients (Table 2). Only 2 of the patients classified later as having RA had no signs of swelling at the initial visit, but developed polyarthritis during the first 6 months of followup. In the non-RA group, there were 4 patients without joint swelling during the 12 months' observation: 3 patients were diagnosed as having reactive arthritis on the grounds of positive cultures of chlamydia and initially slightly elevated acute phase reactants; the remaining patient had a repeatedly positive RF and initially presented with morning stiffness of long duration, albeit without swollen or tender joints.

Involvement of hands (pain or swelling of wrists or finger joints) was significantly more frequent in the RA group [59 (89.4%) of the 66 RA patients] than in the non-RA group [25 (60%); $p = 0.0006$, Fisher's exact test]. Pain or swelling of MTP joints was noted with similar frequency in the RA and non-RA groups (57.6% and 54.8%, respectively).

Early RA cohort

DMARD use. DMARD were used at the discretion of the individual centers. DMARD were used in 57 (86.4%) of the 66 RA patients for whom followup data for at least one year are available. At the time of the one year visit, 21 patients received MTX, 14 sulfasalazine, 7 chloroquine, 4 a combination therapy with chloroquine and MTX, and one each was treated with leflunomide, azathioprine, cyclosporin A, and OM-8980[45]. Thus, 16 RA patients did not receive any DMARD at the one year visit: 9 (13.6%) never took DMARD (for reasons of compliance, 6 of these patients were treated at least intermittently with steroids), and 7 had stopped because of clinical improvement after short courses of sulfasalazine (2 patients), OM-8980 (one patient), or chloroquine (4 patients) in addition to low dose steroids. The remaining 50 patients were treated with DMARD for at least 6 months (documented at at least 3 consecutive visits) during the first 12 months of the study. Among the 49 patients who received DMARD treatment within the first year of RA, the time span to initiation of DMARD therapy from onset of symptoms was 19 ± 10 weeks (mean ± SD, range 4 to 60). Although the RA patients who took DMARD continuously were started earlier than the patients with intermittent use (mean 19 vs 24 weeks), this difference was not significant. The majority of RA patients who received

Table 2. Clinical variables at the initial visit. Tender and swollen joint counts at baseline were significantly different between RA and non-RA patients, whereas pain and disease activity as assessed by visual analog scales (VAS) (in mm) were similar in the both groups (2-tailed t test).

	Swollen Joints	Tender Joints	VAS Pain	VAS Disease Activity (assessed by patient)	VAS Disease Activity (assessed by physician)
RA (n= 52, mean ± SEM)	7.9 ± 0.7	9.8 ± 0.8	49.1 ± 2.4	48.5 ± 2.7	44.8 ± 2.3
Non-RA (n = 33, mean ± SEM)	4.4 ± 0.7	6.0 ± 0.8	53.0 ± 4.1	46.6 ± 4.0	40.9 ± 3.5
p	0.0011	0.0037	0.39	0.68	0.34

DMARD started treatment within the first 6 months from onset of symptoms (Figure 3).

Glucocorticoids. Of the 66 patients diagnosed as having RA and followed for at least one year, 46 (69.7%) were treated with steroids (mostly low dose, ≤ 10 mg prednisone equivalent/day) at some point. In 13 of them (19.7%) continuous use was documented (at 3 or more consecutive visits during the first year). Intermittent use was seen in 33 (50%) RA patients during the first year. Twenty RA patients (30.3%) received no glucocorticoids during their first year of disease.

Overall clinical response. Indicators of disease activity, such as swollen and tender joint counts and acute phase reactants, gradually and significantly ($p < 0.001$) decreased during the first year (Figure 4). In parallel, the Disease Activity Score 28 joint count (DAS 28)[46], a composite measure of disease activity, decreased significantly during the first year (Figure 5A).

The proportion of patients with early RA fulfilling the ACR response criteria is given in Figure 5B. There was an increase in the number of patients who had ACR 20 and 50 responses over time. Among the patients who had an ACR 20 response during at least 6 months of the first year of observation, 92% were treated with either DMARD alone (46%), steroids alone (5%), or both (41%).

Radiographs. Radiographs of hands and feet of each patient were taken at the initial visit and one year thereafter; 63 patients had a complete set of radiographs, 47 (71%) RA patients and 16 (38%) non-RA patients.

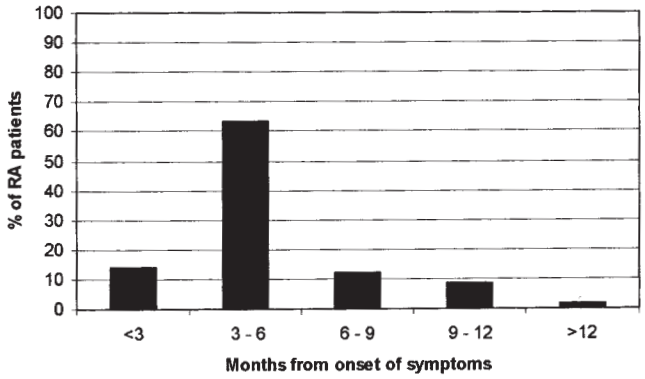

Figure 3. Time to initiation of DMARD therapy. Of the 57 patients followed for over one year who were treated with DMARD, more than 75% started therapy within 6 months of disease (i.e., from onset of symptoms).

Among the 47 patients with very early RA and one year radiological followup, 6 (12.8%) had erosions at the first visit. In 10 additional RA patients nonerosive signs of joint involvement (mainly soft tissue swelling) were seen at visit 1. After one year, 7 additional patients had developed erosions, for a total of 13 (27.6% of all early RA patients) (Figure 6A).

The mean Larsen score per patient (± SD) at the initial visit was 3.5 (± 6.6). After one year, the mean Larsen score increased to 6.3 (± 10.9) (mean increase of 3.6; 95% CI 0.0–5.5, $p < 0.05$ by paired t test).

Three of the 6 RA patients with erosions at visit 1 were RF negative. They reported a duration of their symptoms of 4, 10, and 12 weeks before the first visit, respectively. One of them responded quickly to low dose steroids, so that no DMARD treatment was started during the first year. The other 2 patients started treatment with MTX and chloroquine, respectively, during the first year. The radiological findings in hand and foot radiographs of all 3 RF negative individuals remained unchanged after the first year. The 3 RF positive patients with erosions at baseline reported 12 weeks (2 patients) and 8 weeks (one patient) of symptoms at visit 1. The 2 individuals who were treated with DMARD (chloroquine and MTX/cyclosporine, respectively) had no progression of radiological lesions during the first year. The third patient was seen once and returned for her next followup visit only after 15 months, when she was given a combination therapy of sulfasalazine and MTX. This patient's radiographs revealed progression (new erosions in previously swollen joints and newly developing joint space narrowing in several other joints; the Larsen score at first visit was 30, after 15 months, 40) over the period in which she had remained untreated.

Of the 7 RA patients who had no erosions initially but developed erosive disease during the first year, 6 (86%) were RF positive. All these patients were treated with DMARD (MTX or sulfasalazine, 3 patients each; MTX/chloroquine in combination, one patient) during the first year. Among the 34 patients with RA who did not have erosions at baseline and did not become erosive during the first year of their disease, 13 (38%) were RF positive; 33 of

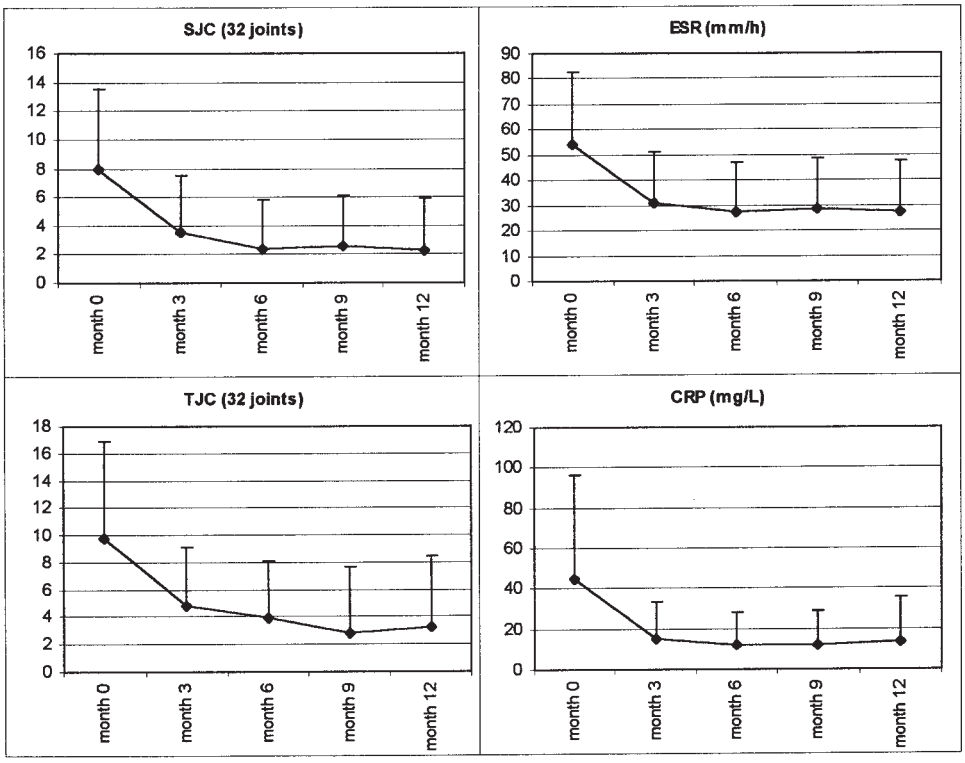

Figure 4. Selected core set variables over time. Clinical as well as laboratory indicators of disease activity showed a continuous and significant decrease over the first year (means + SD; $p < 0.001$ for all variables Month 12 vs Month 0). SJC: swollen joint count, TJC: total joint count, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein.

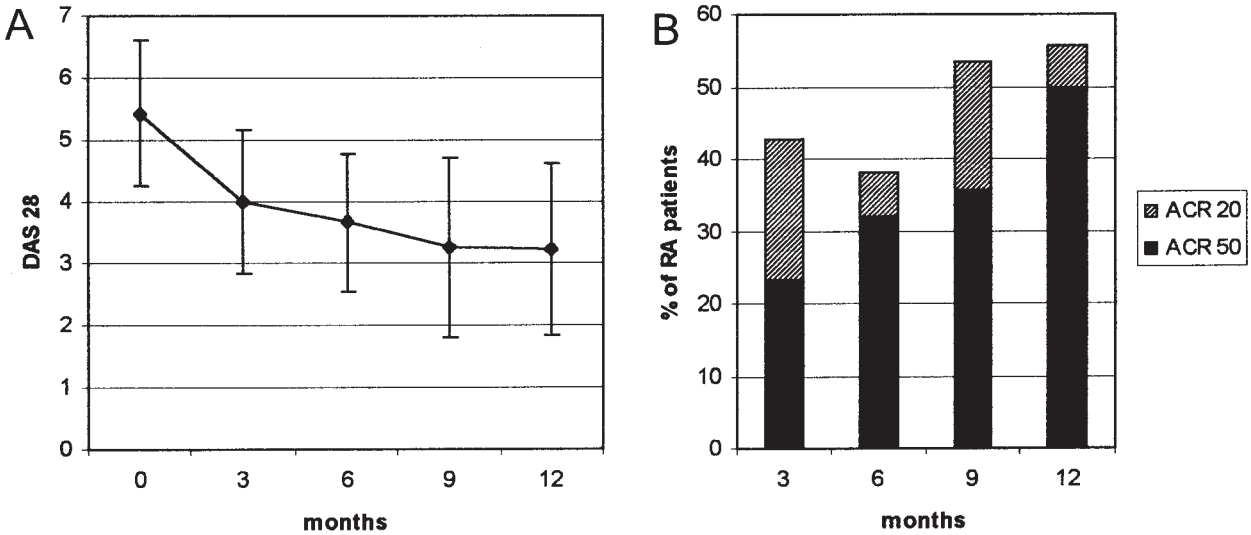

Figure 5. Clinical activity and response criteria in patients with early RA. Over the first year, a decrease of disease activity (DAS 28, A) was evident. The decreases between Months 0 and 3 and between Months 3 and 6 were statistically significant ($p < 0.0001$ and $p < 0.05$, respectively; means ± SD). There was an increase in the proportion of patients fulfilling the ACR response criteria (B).

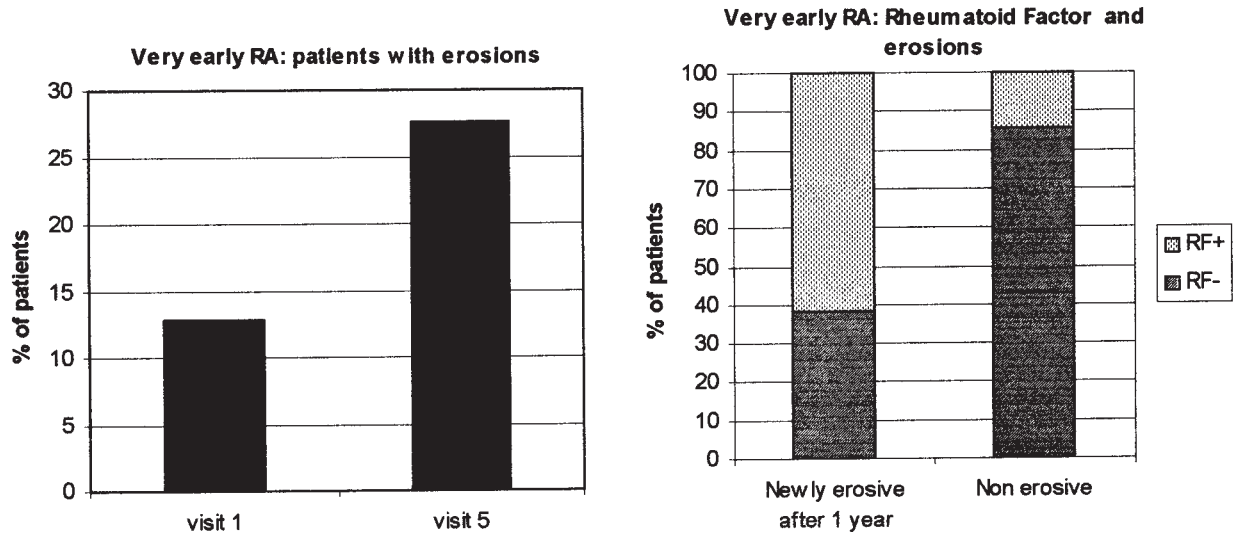

Figure 6. Radiological damage in patients with RA. A. During the first 12 months, the percentage of RA patients with erosions increased; 50% of patients with newly developed erosions had radiological signs of joint involvement at the first visit, the remaining patients had normal radiographs at visit 1. B. There was a strong association between RF positivity and development of new erosions during the first year of disease in patients with RA (OR 9.7, 95% CI 1.05–89.93, $p < 0.05$).

these 34 patients were treated with DMARD during this period. In addition to DMARD, 20 of the patients with nonerosive RA were treated with steroids for some time during the first year. Thus, the risk to develop new erosions during the first year of disease in early RA tended to be related to the presence of RF ($p < 0.05$; odds ratio 9.7, 95% CI 1.05–89.93; Figure 6B).

None of the other disease measures routinely monitored in this study (CRP at presentation, cumulative CRP, ESR at presentation, swollen and tender joint counts) was significantly different between the patients with erosive and nonerosive disease (data not shown).

DISCUSSION

We examined the clinical and radiological findings in a patient cohort seen in very early arthritis clinics (VEAC)[35]. Access was limited to patients with symptom duration up to a maximum of 3 months. Thus, the data in this report offer the unique opportunity to analyze findings in the very early period of inflammatory joint disease.

In planning the EAA it was expected that a considerable number of patients would be referred for musculoskeletal diseases other than RA. However, among the patients enrolled, the proportion of patients classified as having RA was surprisingly high, in the order of 50%. Nevertheless, some of the other diseases for which the patients were referred also required rapid attention to prevent irreversible damage, such as SLE, polymyositis, or psoriatic arthritis. Since the inclusion criteria required an individual to show at least one laboratory sign of inflammation, such as levels of CRP or ESR above upper normal limits[35] or positive RF, "noninflammatory" arthropathies ("arthralgia," osteoarthritis) were diagnosed in only a small fraction of patients (about 6% of all referrals). This may also explain why a relatively large proportion of RA patients were included into the study. A large proportion of the non-RA group, however, had undifferentiated or seronegative arthritides.

Despite the early appearance of the referred patients' diseases, a diagnosis of RA was already suspected in more than 65% of the patients at the time of the initial visit. In only one-third of the RA population seen for at least one year were other diagnoses (or no definitive diagnosis) suspected at the initial visit. It should be borne in mind, however, that there are no validated classification or diagnostic criteria for early RA. Thus, although care was taken to exclude only other defined conditions, occasional patients with subsequent RA may have been excluded. However, the frequency of RA in this study is similar to that seen in other cohorts[22,30]. Moreover, at the time of the second visit, i.e., within 6 months after onset of symptoms, a diagnosis was established in 90% of the RA patients, leaving only 10% who had to await diagnosis longer than 6 months. Some patients in the RA group presented with symptoms of less than 6 weeks' duration (the ACR classification criteria call for presence of signs and symptoms for at least 6 weeks). Nevertheless, in 9 of these 16 patients (56.3%) RA was already suspected at the first visit (all on the basis of polyarthritis of the hands) and was confirmed during followup. Overall, we are aware that terminology in early disease is a difficult issue and that future consensus will be needed on terminology, such as the terms "early RA" or maybe more appropriately "early inflammatory arthritis"[47].

One of the problems of approaching patients with RA early is the lag period between onset of symptoms and

referral to a rheumatologist. The reason for this lag period may be lack of appreciation of the features inherent to the disease by both patients and their primary physicians (mostly general practitioners). In this study, we found a significantly longer lag period to referral for RA (mean of 8 weeks) as compared to non-RA patients (mean of 6 weeks). An important reason for this significant difference could be the observation that RA patients frequently regarded the onset of their symptoms as insidious, while the non-RA patients frequently reported an acute onset. Thus, one important lesson from the study is the need to inform patients that even insidiously starting joint disease requires rapid attention by a rheumatologist.

Almost 50% of the RA patients did not fulfil ACR classification criteria for RA at presentation to the rheumatologist. Conversely, almost 20% of the non-RA patients would have fulfilled these criteria and almost 20% of the "ACR positive" patients had tentative diagnoses other than RA at presentation. Even when "cumulative fulfillment" of the ACR criteria was evaluated, as has been suggested[44], only 51 (77%) of the early RA patients in the present cohort would have been classified as having RA. This is in agreement with the observation of others[30,44,48] and points to the need for classification or diagnostic criteria that better differentiate RA from non-RA, or even more important, destructive and thus possibly debilitating disease from more benign entities in the early phases of the disease. Steps in this direction have been made by several authors[22,30,48,49], but no valid and practical consensus has been reached yet. Validation in multicenter and if possible, multicultural settings for such a set of criteria would be required. One reason why roughly one-fifth of the RA patients in our cohort never fulfilled the full set of criteria for classification of RA during the first year may lie in the fact that all these individuals received DMARD (10 patients) or steroids (2 patients) or both (3 patients).

RF was positive in 51% of the RA patients at their first visit. However, RF was also found in 15% of the non-RA population, confirming that this test has its limitations in differentiating early RA from early non-RA disease; other laboratory markers should be considered in this respect. Indeed, a subgroup of our RA patients has been tested for RF, and for antibodies to hn RNP-A2 (RA33) and SA, and the results revealed the complementary nature of these assays[50]. Only 2 patients converted from RF seronegative to seropositive. Since the presence of RF tends to increase with disease duration but decreases with effective therapy[51,52], the "failure" to detect an increase in RF frequency over time suggests that the therapeutic approaches taken may have been quite successful. This is corroborated by the significant reduction of indicators of disease activity such as joint counts, acute phase response markers, and the DAS 28 over time. Also, by one year a significant proportion of patients (59%) fulfilled the ACR 50% response criteria.

An association between erosive disease and the presence of RF has been established in numerous studies. The low frequency of erosive disease despite a frequency of RF comparable to that found in other early RA cohorts[22,29,48] is in accord with the early nature of the disease in the present cohort. However, of all patients developing new erosions within the first year, 85.7% were RF positive, compared to 38.2% of the nonerosive patients followed over one year. This further supports the importance of RF as a risk factor for erosive disease[22,30,48]. In addition, even in these patients who were diagnosed very early (and treated mostly with DMARD or steroid) erosions developed during the first year. This underscores the importance of the observations that considerable damage occurs already at these very early stages. Conversely, despite their seropositivity, 59% of the RF positive patients did not develop erosions during the first year, probably an indication for successful early DMARD therapy.

It has been shown by several investigators that joint destruction is a relatively early event in RA: up to 40% of patients develop erosions within the first year[18,53]; this number increases to 70% later[19]. Also, the number of eroded joints appears to increase at the fastest rate within the first 2 years of disease[18,19,53]. In our study, only 12.8% of the RA patients had erosions at presentation. This low percentage not only confirms the very early stage of RA studied here, but also suggests that the majority of erosions do not occur at a preclinical stage of disease, even if histological changes can be seen before clinical joint involvement[2]. In addition, only one of these 6 patients, the only one who did not take DMARD for reasons of compliance, showed progression of erosive disease during the first year of followup.

Despite early DMARD therapy, 7 of the 41 patients without erosions at entry developed erosions within one year. This suggests that even more aggressive therapy may be required in some patients in the early stages. However, for such a decision, risk factor analysis will be needed, which will be a focus in the continuation phases of the EAA. On the other hand, erosions would be expected in up to 40% of the patients after 12–15 months from onset of disease. Thus, our findings suggest that the development of radiographic changes was prevented in a large fraction of RA patients in conjunction with the very early introduction of DMARD, at least for the first year. This points to a true "window of opportunity" with respect to the prevention of joint destruction in RA.

In conclusion, our study in very early arthritis revealed that (1) patients with RA tend to be referred later than other patients, possibly due to the insidious onset of their joint disease; (2) RA may be diagnosed early; (3) patients with RA at early stages tend to have a relatively low frequency of joint damage; (4) development of erosions over the first year is associated with RF; (5) very early DMARD therapy leads to high responder rates, suggesting the existence of a "ther-

apeutic window" of time when the course of the disease can be altered substantially. Continuing followup of our patient cohort will be carried out to learn more about the longterm fate of patients followed from very early stages in the course of their disease.

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