The Austrian Early Arthritis Registry

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ABSTRACT

The Austrian Early Arthritis Registry (Austrian Early Arthritis Action, EAA) enrolls and follows patients with inflammatory arthritis of very short (< 12 weeks) duration. Currently, data on 375 patients (almost 2000 individual follow-up examinations) have been entered into the EA database. Evaluations of data from 182 patients with a follow-up of at least one year are available. 65% of these patients have RA, as diagnosed using the ACR classification criteria in a cumulative fashion. Approximately 15% of these patients still have no established diagnosis and are being carried forward and observed as cases of "undifferentiated arthritis". In RA patients, the mean DAS 28 decreased significantly from an initial mean score of 5.5 (high disease activity) into the range of low disease activity. At the end of one year a DAS 28 of <3.2 was observed in 52% of the RA patients. Radiological progression in these RA patients, who also received treatment very early, appears to be less severe than in other cohorts, although direct comparisons are impossible due to different methods of patient selection. In addition, the serological data from our cohort in cooperation with other study groups will allow development and validation of possible prediction algorithms for early arthritis patients which could improve the diagnostic and therapeutic approach to this patient group.

Introduction

Early arthritis clinics (EACs) have been established to facilitate as early as possible the diagnosis and therapy of rheumatoid arthritis (RA), and other potentially destructive arthritides, given the risks this disease poses to quality of life and mortality (1-4). This relatively straightforward concept encounters major difficulties in practice however: (i) Classification criteria for RA have been developed on the basis of established disease (5). (ii) Destructive arthritis (in particular RA) is often difficult to diagnose in the early stages because of its frequently "atypical" (e.g. oligoarticular) presentation, and may not meet classification criteria. (iii) Standard serologic markers, such as rheumatoid factor, are frequently negative in early RA and plain X-rays detect erosions long after the underlying structural damage has begun. (iv) The majority of patients with RA are initially seen by non-specialists, most of whose experience with musculoskeletal disease involves soft tissue arthritis, fibromyalgia, post-traumatic arthritis, or osteoarthritis, and therefore may not be fully cognizant of this potential diagnosis or may not be aware of the risks of misdiagnosis, and thus inadvertently delay proper referral and therapy. In fact, surveys among European rheumatologists have indicated that a substantial number of patients are usually seen in rheumatology clinics or practices more than six or even twelve months after the onset of disease (6). In contrast EACs, by virtue of their very nature, will include many pa-tients with diseases other than destructive arthritides.

The Austrian Early Arthritis Registry

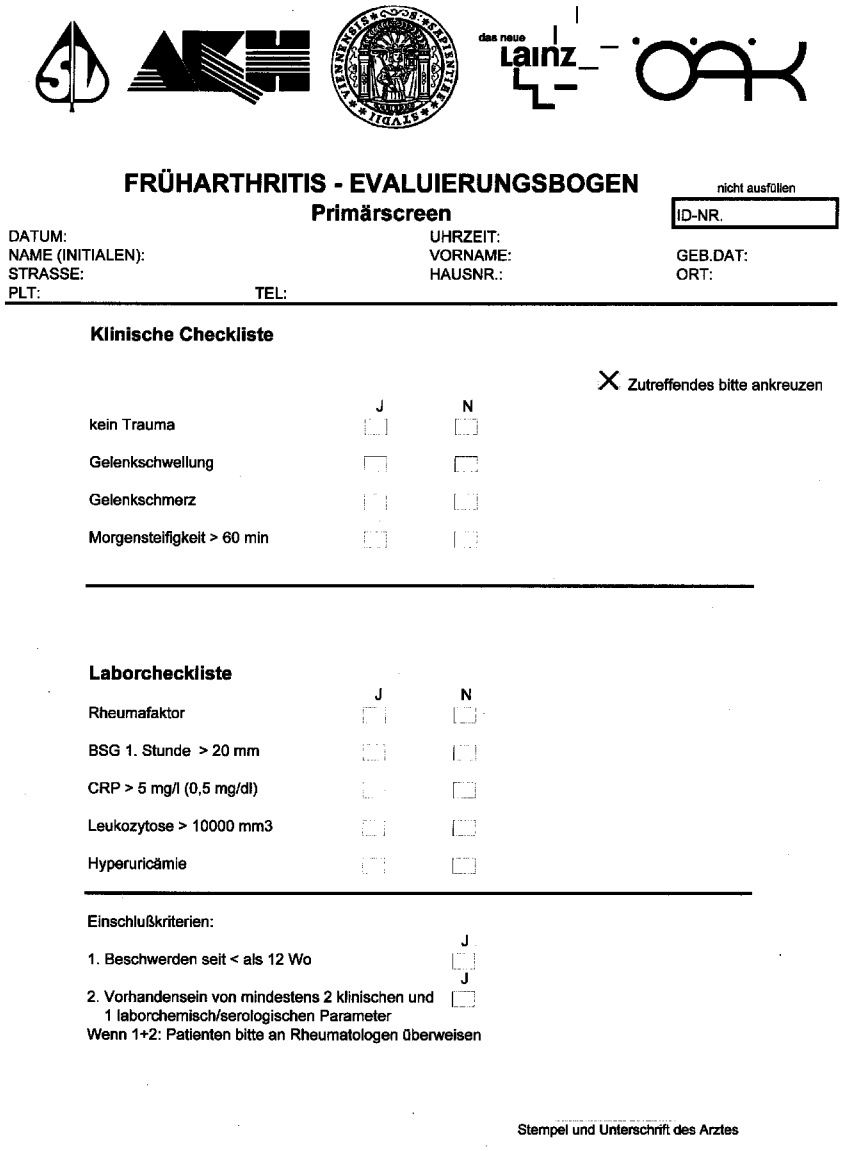
The Austrian "Early Arthritis Action" (EAA) was initiated in 1995 as a nation-wide endeavor. As inclusion criteria we chose a set of easily recognizable clinical characteristics and in addition a very stringent limit on the duration of symptoms from onset, namely 12 weeks (Table I). In order to facilitate access to specialized rheumatology care for these patients, a "fast track" referral procedure was established at the outpatient clinics of participating centres, by which means the average waiting time was reduced to less than two weeks.

Recognizing the potential problems that could hinder early referral, a number of steps were taken to transfer information to practitioners, internists, and the general public: (i) Approval and support was sought and obtained from the Austrian Chamber of Physi-

Table I. Inclusion criteria for the Austrian Early Arthritis Action.

Inclusion: Patients fulfilling ≥ 2 clinical AND ≥ 1 laboratory criterion AND duration of symptoms ≤ 12 weeks.	
Clinical:	1. Absence of trauma
	2. Joint swelling in at least 1 joint
	3. Joint pain in at least 1 joint
	4. Morning stiffness > 60 minutes
Laboratory:	1. Positive rheumatoid factor
	2. ESR > 20 mm/h
	3. CRP > 5 mg/L
	4. Leucocytes > ULN

cians, the National Council of Social Security Agencies, and the Ministry of Science and the Ministry of Health. (ii) A series of educational articles was published in the official journal of the Austrian Chamber of Physicians, the *Österreichische Ärztezeitung*, which is distributed to every physician in the country. (iii) In early 1996, EACs were officially and jointly established at two departments: the Division of Rheumatology at the University of Vienna and the Centre of Rheumatic Diseases, 2nd Department of Medicine at Lainz Hospital in Vienna; (iv) Approximately 30 additional departments specialising in the care of patients with rheumatic diseases were invited and agreed to participate in the EAA and to establish EACs; co-operation with at least one department in every one of the 9 federal states of Austria was established. All participating centres were provided with full length forms for obtaining a standardised history and clinical examination of each patient, which were supposed to be completed every three months. (v) The "primary questionnaires" were distributed by means of the *Österreichische Ärztezeitung* in early 1996. (vi) A press conference was held at the end of February 1996 followed by articles in the mass media about the EAA. Thus, general information on signs and symptoms suggestive of arthritis was provided, and affected individuals were requested to contact their family physicians and, in the case of suspected arthritis, to ask for further referral to one of the nationally distributed EACs. The EAA finally started on March 1, 1996.



FRÜHARTHRITIS - EVALUIERUNGSBOGEN

Primärscreen

nicht ausfüllen

ID-NR.

DATUM: UHRZEIT:

NAME (INITIALEN): VORNAME: GEB.DAT:

STRASSE: HAUSNR.: ORT:

PLT: TEL:

Klinische Checkliste

X Zutreffendes bitte ankreuzen

	J	N
kein Trauma	☐	☐
Gelenkschwellung	☐	☐
Gelenkschmerz	☐	☐
Morgensteifigkeit > 60 min	☐	☐

Laborcheckliste

	J	N
Rheumafaktor	☐	☐
BSG 1. Stunde > 20 mm	☐	☐
CRP > 5 mg/l (0,5 mg/dl)	☐	☐
Leukozytose > 10000 mm3	☐	☐
Hyperuricämie	☐	☐

Einschlußkriterien:

1. Beschwerden seit < als 12 Wo J ☐

2. Vorhandensein von mindestens 2 klinischen und 1 laborchemisch/serologischen Parameter J ☐

Wenn 1+2: Patienten bitte an Rheumatologen überweisen

Stempel und Unterschrift des Arztes

Fig. 1. The primary questionnaire (PRIQ, "Primärscreen") which was distributed to interested physicians throughout the country

Questionnaires and assessments

The "primary questionnaires" (PRIQ, Fig. 1) were devised to help non-specialist physicians differentiate between inflammatory and non-inflammatory rheumatic diseases. The procedure for enrolling patients is the following.

Patients who fulfil the entry criteria and have symptoms for less than 12 weeks should be referred to one of the co-operating specialised rheumatology centres that has been provided with the "full length questionnaire" (FLEQ) containing all pertinent questions regarding the patient's medical history, clinical findings, laboratory investigations and radiological assessments as well as drug therapy (current and past) and its efficacy. There the patients are (re-)assessed and entered into the EAA, if early arthritis is confirmed. After the initial evaluation, FLEQs are be completed by the rheumatology centres every three months. In addition, an Austrian version of the HAQ is completed by the patients at every visit. In patients suspected of having RA, X-rays of the hands and feet (in addition to other affected joint regions, if any) are performed every 12 months. The PRIQs and FLEQs are mailed to one of the two main centres of the EAA for analysis. X-rays are analysed on a periodic basis using established scoring me-

Table II. Diagnoses of patients followed for at least one year.

Diagnosis (according to the patient's rheumatologist and chart review)	No. of pts.
Rheumatoid arthritis	120
Undifferentiated arthritis	23
Reactive arthritis	22
Psoriatic arthritis	3
Seronegative SpA	3
Sarcoidosis	2
Palindromic rheumatism	2
Polymyalgia rheumatica	2
Collagen vascular disease (except SLE)	2
Crystal arthritis	1
SLE	1
Osteoarthritis	1

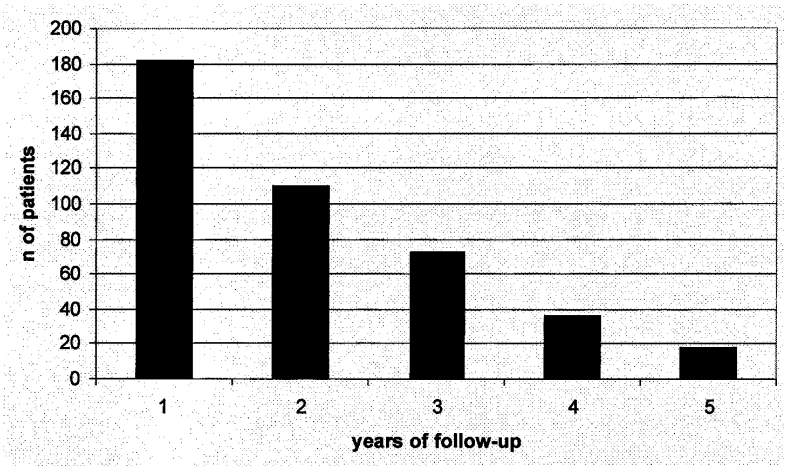


Fig. 2. Duration of follow-up and respective numbers of patients followed.

thods and the results linked to the clinical data.

Data from all patients are then entered into a database, all patients having given their consent to this data acquisition. In addition to routine laboratory tests, patients are asked for blood samples (for specialized investigations) at entry into the study, for which specific consent is obtained. Blood samples are stored at the co-ordinating centres.

Issues related to nation-wide cooperation

In the ensuing years it proved quite difficult to recruit patients at most of the centres. Although all of these centers participated voluntarily and several centers even undertook activities to become partners in this endeavour, there are several possible explanations for these difficulties. Firstly, it may simply be too tedious for many rheumatologists working in out-patient clinics to fill out forms regularly on a voluntary basis, to motivate patients to fill in HAQ questionnaires, and to provide a central registry with the information. Secondly, wittingly or unwittingly, fears of being "controlled" for the quality of the diagnostic process may add to their hesitation. Thirdly, more than one third of the population are living in rural/alpine regions with rather limited access to specialist care (source: "Statistik Austria" website, http://www.statistik.at/) and many patients with early arthritis may present themselves at a clinic with a delay in excess of the 12-week deadline for entry into the registry. Fourthly, despite the increasing availability of communication media and despite our best efforts to exploit these media, the awareness of the population (and of general practitioners) of the problems posed by arthritis remains rather low, and medical help is sought relatively late. Fifthly, even if all the factors come together positively, the rheumatologists at the participating centers may simply "forget" to enter the patient(s) into the registry. During the initial months of the EAA only three centres located in Vienna recruited substantial numbers of patients; many centers around the country succeeded in enrolling just a single patient. Thus the vast majority of the patients in the EAA represent a sample of the patient population served by three of the six rheumatology centres in the Vienna area (i.e., half of a population of about 2.5 million) (7).

Table III. Clinical characteristics of early arthritis patients at presentation to the clinic.

a. Means ± SD of clinical core set variables in the RA group versus the non-RA group

	Swollen	Tender	VAS pain	VAS disease activity (patient)	VAS disease activity (physician)
RA	8.4 ± 5.8	10.7 ± 7.2	51.2 ± 18.7	48.2 ± 23.0	44.8 ± 19.4
Non-RA	4.6 ± 4.6	5.4 ± 5.7	59.2 ± 24.5	52.7 ± 24.5	44.6 ± 22.2
p-value (two-tailed t-test)	0.002	0.0003	0.12	0.40	0.97

b. Median symptom duration in the RA group versus the non-RA group

	Symptom duration (weeks)	
	Median	IQR
RA	8	4-10
Non-RA	4	2-8

($p < 0.01$, Mann Whitney test)

Current status of the EAA

As of January 2003, 375 patients had been entered into the EA database. Almost 2000 follow-up examinations have been performed in this cohort, some of the patients having been followed for over 5 years (n = 19, Fig. 2). The data are updated regularly and the entire cohort of patients is evaluated every 1-2 years. The next evaluation will be performed during the second half of 2003. Currently, data from 182 patients with a follow-up of at least one year are available. The diagnoses of these patients are listed in Table II. Not unexpectedly, the majority (65%) of

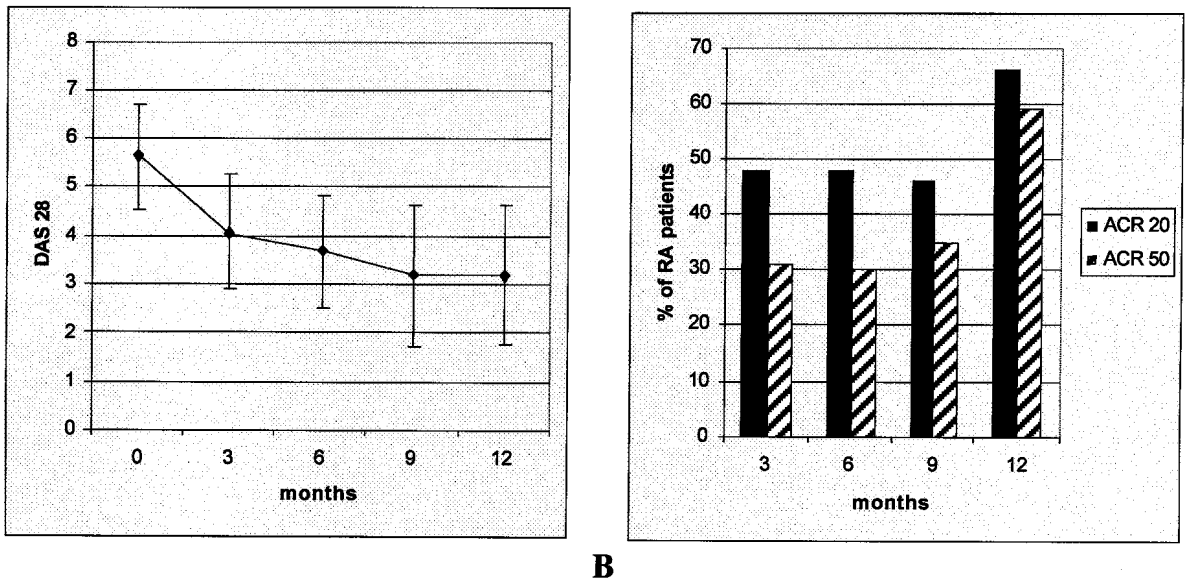


Fig. 3. Clinical activity and response criteria in early RA patients. Over the first year a decrease in disease activity (DAS 28, panel A) was evident. The decreases between months 0 and 3 and between months 3 and 6 were statistically significant ($p < 0.0001$ and $p < 0.05$, respectively; means ± SD).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

the patients followed for ≥1 year turned out to have rheumatoid arthritis [as diagnosed by the primary care physician and ascertained by chart review after one year using the ACR classification criteria in a cumulative fashion (8)]. Approximately 15% of the patients who were followed for longer than the first year still had no established diagnosis and were carried forward and observed as "undifferentiated arthritis".

In accordance with previous observations (8), the clinical characteristics of RA and non-RA patients in this early arthritis cohort were significantly different with respect to the joint counts and elapsed time to referral (Table III). The longer lag time to referral of RA patients was possibly related to the patients' rating of the acuteness of the onset of their arthritis. Overall, 57% of patients in the non-RA group rated the onset of their arthritis as acute, compared to 40% of the RA patients ($p < 0.01$).

Treatment

Within the framework of the EAA, no recommendations for treatment were given, in the hopes of enhancing the compliance of participating physicians and to mimic as far as possible a "real life" situation. Thus, medical treatments encompassed mostly the traditional DMARDs (usually chloroquine, sulfasalazine, or methotrexate) in addition to NSAIDs and glucocorticoids. In the majority of patients (75%), DMARDs were instituted within 6 months from onset. Approximately 60% of the patients received (low dose) glucocorticoids during the first three months. This proportion decreased during the following observation period to 20% at the twelve-month visit.

Clinical data

In RA patients, the therapy instituted led to a reduction in the joint counts, ESR and CRP levels by > 60%. In fact, the mean DAS 28 (9) decreased significantly from an initial mean score of 5.5 (high disease activity) into the range of low disease activity (Fig. 3). Moreover, ACR50% responses (10) were achieved in > 50% of the patients within 1 year. At the end of one year a DAS 28 of < 3.2 was observed in 52% of the RA patients.

These (near) remissions included both successful therapy and spontaneous remission at least in some patients with very early RA. Given that arthritis of ≥ 3 months' duration is usually considered persistent arthritis (11) and that the frequency of 47% RF positivity is well in accordance with data from inception cohorts of RA populations, some with an even longer disease duration, we believe that the clinical outcome reflects a success of this early therapeutic approach. This is further confirmed by data showing that very early DMARD therapy leads to a higher degree of improvement than delayed treatment (12, 13). However, spontaneous remissions do occur in early arthritis, and further evaluation is in progress to investigate this matter.

Radiological changes at baseline and at 1 year

At baseline, 12% of the RA patients in this inception cohort had erosions (Larsen score of ≥ 2 in at least one joint). This proportion of patients increased to 28% by 1 year. Mean (± SD) Larsen scores were 3.5 (± 6.6) initially and 6.3 (±10.9) at 1 year. Since most RA populations have erosive disease in the range of about 40% by 1 year (14-16), these data suggest that the very early institution of DMARD therapy has been quite successful, although some patients progressed nonetheless. Currently, with substantially more patients reaching the 1-3 year thresholds of follow up, the findings are being re-evaluated. In addition, with a larger number of observations it may be possible to determine which clinical characteristics at the very early stage of disease are related to radiological outcomes. In particular, it will be of interest to analyze the possible predictive

prognostic value of serologic and clinical variables, as well as the type of response to treatment (fast versus slow), the type of treatment (one DMARD versus another), or the degree of response (which level of response) that is required to slow or prevent radiographic progression.

Serological investigations

Several serological markers have been studied in patients with rheumatoid arthritis, although only rheumatoid factor (17) has unequivocally been proven to be useful for the diagnosis and prognosis (18, 19). However, other serologic markers such as anti-citrullinated cyclic peptide (anti-CCP) (20) and anti-RA-33 (21) may prove to be more valuable in early RA than in established disease. For example, in a cohort similar to ours in the Leiden Early Arthritis Clinic (see this supplement, Aken *et al.*), anti-CCP, which was included in a prediction algorithm for outcomes of early arthritis, appeared to yield encouraging results (22).

In our cohort, 55% of the RA patients were RF-positive, 41% had anti-CCP and 28% anti-RA33. Anti-CCP and anti-A2 (RA33) antibodies were added to the set of diagnostic items currently applied to rheumatoid arthritis (23), although these antibodies did not appear to have the same value for prognosis in our cohort compared to the Dutch population (24). These findings require further confirmation and clarification, and currently are being extended to larger samples from both our and cooperating groups' populations.

Conclusion

With the Austrian EAA, we have taken an approach to the problem of early recognition, which differs somewhat from other similar approaches in that we enroll and follow only patients at a very early stage of the disease (<12 weeks). Despite the fact that a considerable amount of uncertainty regarding the initial diagnosis is present at this early stage, a definitive diagnosis was made in most patients during the first months of follow-up. In addition, we have demonstrated that symptoms and signs of disease activity improved substantially over time in a substantial number of patients. This appears to be due to the rigorous early therapeutic approach adopted for some patients and may reflect the presence of benign disease in others; perhaps both the factors of milder disease and the benefits of early intervention are present. These matters are under study. However, it should be noted that some patients still seem to do poorly despite very early DMARD treatment. Further research is being directed to identify risk factors for aggressive disease, using serological as well as clinical markers. The findings of these studies will be analyzed in cooperation with other centers caring for patients with early RA to establish their possible generalizability.

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