

Very recent onset rheumatoid arthritis: clinical and serological patient characteristics associated with radiographic progression over the first years of disease

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Objectives. Despite early recognition and disease modifying anti-rheumatic drug (DMARD) treatment, a sizable proportion of early rheumatoid arthritis (RA) patients show radiological progression. This study was performed to determine the frequency of erosive arthritis and the pace of radiological progression in an inception cohort of patients with very early RA (≤ 3 months after onset of symptoms).

Methods. In order to determine possible prognostic factors for development of erosive disease, we linked the clinical features of these patients to radiological progression in a regression model. About 55 patients with RA and follow-up of at least 3 yrs were analysed. All had complete series of clinical, serological and radiographic assessments. Radiographs were scored according to the Larsen method.

Results. Erosive disease developed in 63.6% of the patients over 3 yrs, with the majority (74.3%) appearing already in the first and 97.2% by the end of the second year. Among all variables available, rheumatoid factor (RF) and/or anti-cyclic citrullinated peptide (anti-CCP) first presentation were the most predictive for both development of erosions and the degree of radiological progression. None of the clinical variables at the onset was useful to discriminate between erosive and non-erosive patients. In the final regression model, however, cumulative clinical activity substantially contributed to explaining radiological progression.

Conclusion. Despite early treatment, substantial damage occurred in some patients and was associated with presence of strong 'constitutive' predictors such as anti-CCP and RF as well as presence of high long-term clinical disease activity as indicated by C-reactive protein (CRP), swollen joint counts and the absence of a good clinical response (assessed by the failure to achieve lasting low disease activity).

KEY WORDS: Very early rheumatoid arthritis, Determinants of radiographic progression, Disease control.

Introduction

In recent years, it has been postulated that early intervention improves the outcome of rheumatoid arthritis (RA) over both short- and long-term [1–3]. Early treatment may become even more advantageous for the patients if it is intensive and dynamic compared with more conventional treatment approaches [4–6].

Most clinical studies on early RA included patients with disease durations of 1–3 yrs at baseline. Although this period is relatively short considering that RA may last for decades, the fundamental pathophysiological mechanisms of the disease, namely the propensity to erode and thus destroy joints, probably have become firmly established at one or more years after onset. In fact, up to 60% of the patients have joint erosions at the end of 1 yr from disease onset [7–9], and more than 10% have joint erosions when presenting even as early as at a median of 8 weeks from emergence of symptoms [10]. Thus, it appears that the disease process, at least in some patients, may start before the actual onset of symptoms, and this is supported by the presence of characteristic autoantibodies long before disease manifestation

[11–13]. The fact that joint damage progresses in many early RA patients even during disease modifying anti-rheumatic drug (DMARD) therapy may be a possible consequence of such early disease determination towards destruction. In fact, even when DMARDs were instituted 'very early', some patients developed erosions or had progressive joint damage [1, 3, 14].

However, currently it is still difficult to predict who among the patients with early or very early RA will have progression of their disease. Such information would be important for optimizing treatment strategies. The present analysis was undertaken to determine which serological markers or clinical indicators of disease activity are related to the development of erosions over 3 yrs in a cohort of patients with RA who were seen (and treated) by rheumatologists very early.

The very early arthritis cohort presented here is notable in the sense that it includes only patients with symptom duration of <12 weeks. This strict inclusion criterion followed clues that arthritis is likely to become persistent after 12 weeks of symptoms [15–17] and the majority opinion among rheumatologists participating in recent surveys suggested that arthritis of >3 months

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symptom duration should not be regarded as early [18]. Such a cohort of patients, when followed over the years, allows to discern not only the fate of very early inflammatory joint disease under specific therapeutic conditions, but also to attempt to determine predictive factors during the early stages of the disease.

The specific aims of this study were (i) to determine the frequency of erosive arthritis among patients with very early RA; (ii) to describe the clinical features of patients diagnosed as RA who did not progress to developing erosions or new erosions; (iii) to determine the pace of progression of radiological changes during the first 3 yrs of disease; and (iv) to link radiological progression to clinical and serological variables, and thus to determine possible prognostic factors for development of erosive disease.

Patients and methods

Details of the Austrian Early Arthritis Action (AEAA) have been described elsewhere [19]. This initiative focuses on very early arthritis patients (<3 months from onset of symptoms to first presentation to the rheumatologist). Patients were seen in the out-patient clinics of the Vienna General and the Municipal Hietzing Hospitals. Approval was obtained from both institutions' ethical committees. The study was conducted according to the guidelines of the Declaration of Helsinki; informed consent for participation was obtained in writing from every participant.

Patients

All patients presenting with early arthritis were included in the AEAA-cohort. 'Early arthritis' was defined as two of the following four clinical criteria: no trauma, at least one tender joint, at least one swollen joint, morning stiffness lasting for at least 60 min; in addition, serological signs of inflammation [elevated erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP)] or rheumatoid factor (RF) positivity and a symptom duration of no longer than 12 weeks were inclusion criteria.

In the early arthritis cohort from 1996 to 2001, 314 patients were included. Of these 314 patients, 85 were seen only once and did not return for a follow-up visit. Among the remaining 229 patients who had at least one follow-up visit and were given at least a tentative diagnosis, 91 had a diagnosis other than RA. Their diagnoses were as follows: reactive arthritis 40 (44%), undifferentiated arthritis 26 (29%), osteoarthritis 4 (4.4%), gout, psoriatic arthritis, palindromic rheumatism 2 (2.2%) each, rheumatic fever, sarcoidosis, polymyalgia rheumatica, SLE and polymyositis 1 (1.1%) each.

Among the 138 patients diagnosed as RA, several did not return for further evaluation during the first ($n=18$), second ($n=38$) and third ($n=27$) year. Thus, 55 patients with RA had radiological follow-up of at least 3 yrs in 2004 (Fig. 1). At least three sets of radiographs of the hands and the feet were available for each patient, including baseline and 3-yr-follow-up. These patients constitute the focus of this study. The mean age (\pm s.d.) of the patients was 50.9 ± 14.78 yrs, range 23–77 yrs; 14 (25%) patients were male.

As in other early arthritis cohorts, cumulative fulfilment of American College of Rheumatology (ACR) criteria for RA was used for diagnostic purposes [10, 20]. Moreover, all diagnoses were ascertained by chart review. According to the protocol, treatment was not pre-defined but the choice of therapy was left to the discretion of the treating physicians in order to simulate a 'real-life'-like situation.

Clinical assessments

At the first visit and every 3 months thereafter, clinical assessments included 28 joint counts for swelling and tenderness,

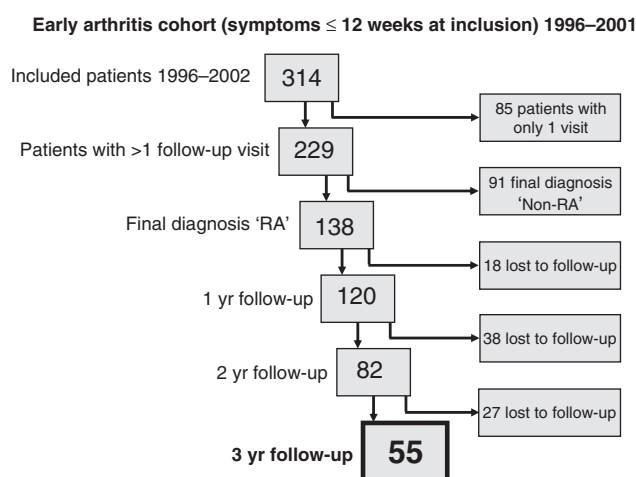


FIG. 1. Follow-up of the patients included into the early arthritis cohort between 1996 and 2001.

health assessment questionnaires (HAQ), assessments by visual analogue scales (VAS) for pain, global disease activity by the patient and the evaluator, i.e. patient global assessment (PGA) and the evaluator global assessment (EGA). In addition, blood was drawn for routine chemistry and haematology as well as for ESR, CRP, RF and yearly determination of anti-CCP antibodies. A DNA sample for determination of the shared epitope was also obtained.

X-rays

Plain radiographs of both hands and forefeet were obtained at baseline and yearly thereafter. All X-rays (pa views) were read by two experienced readers (M.U. and K.P.M.) and scored according to the method described by Larsen *et al.* [21] which was modified by Scott *et al.* [22] with weighted scoring for the wrist. This method yields scores from 0 (absence of any destructive change) to 168 (maximum destruction in all scored joints). For the classification of patients as having erosive RA, erosions were defined as follows: presence of at least one unequivocal lesion on any hand or foot joint except the distal interphalangeal (DIP) joints with an unequivocal cortical break of at least 1 mm in width or, if the erosion or the cortical break was smaller, presence of at least two such lesions of different joints [23]. Reading sessions were held with both readers present. Disagreements in assessments were resolved immediately by consensus. Each patient's radiographs were read as sets of films with known sequence but with the readers blinded to the identity of the patients [24]. A subset of radiographs was read twice in order to ascertain precision of the readings; agreement between the assessments was found to be good (Spearman correlation coefficient 0.86, 95% CI: 0.81–0.91).

Laboratory measurements

ESR was determined by a modified Westergren method, CRP and RF were determined by nephelometry. Anti-CCP antibodies were measured by (second generation) enzyme-linked immunosorbent assay (ELISA, Axis Shields Diagnostics) and considered positive at a cut-off value >5 arbitrary units as suggested by the manufacturer.

Shared epitope

HLA-DRB1 typing and subtyping was done by polymerase chain reaction (PCR) on DNA extracted from EDTA-whole blood. For alleles *0101, *0102, *0104, *0401, *0404, *0405, *0413, *0416 and *1001, which are the 'shared epitope alleles' [25], sequence specific oligonucleotides were used after low-resolution DRB1 typing.

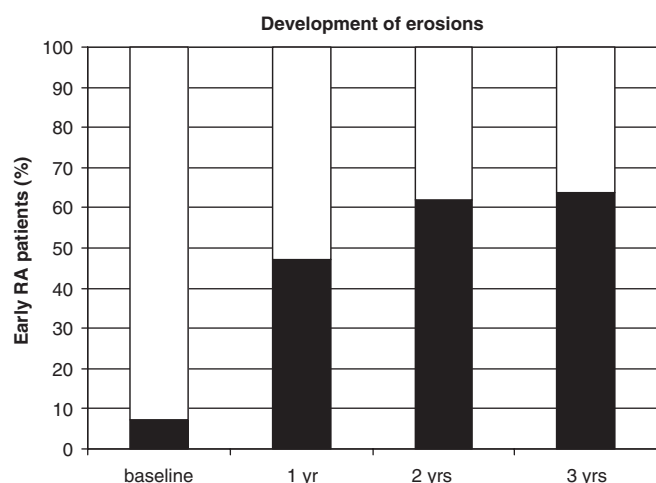


FIG. 2. Cumulative appearance of erosions in the 55 early RA patients.

Statistical analysis

Because of their mostly non-normal distributions, continuous variables were analysed using Mann–Whitney *U*-test, and categorical variables were analysed using Fisher's Exact test. For analyses requiring normally distributed variables, mathematical transformations were performed which resulted in Gaussian distributions.

In univariate analyses, Spearman correlation coefficients between Larsen score progression and (i) autoantibodies, (ii) the shared epitope and (iii) the clinical variables were calculated. In order to reflect the temporal (cumulative) dimension of clinical and laboratory parameters as well as the disease activity score including 28 (DAS28), areas under the curve (AUC) were calculated using the trapezoid rule. In the case of missing values, these were replaced by the last observation (carried forward). In addition, we estimated the duration (in months) each patient spent in high, moderate or low disease activity or remission indicated by the DAS28 score according to the published criteria [26, 27] and also using the simplified and clinical disease activity indices (SDAI and CDAI) [28, 29].

In addition, on the basis of these univariate analyses, a stepwise regression model was derived to account for the highly significant association of RF and anti-CCP with the degree of progression.

All data analyses were carried out using SPSS V 12.0 (SPSS GmbH Software, München). *P*-values below 0.05 were considered statistically significant.

Results

Development of erosive disease

Four patients had erosions already at baseline, 26 after 1 yr, in four patients radiographic erosions first appeared in the 24 month X-rays and one patient developed erosions during the third year; thus, over the observation period of 3 yrs, 35 of the 55 patients (63.6%) developed erosive disease. Erosions mostly became manifest during the first year of the disease, despite DMARD therapy (Fig. 2).

Treatment

The choice of treatment in this cohort according to the protocol was left to the discretion of the treating physicians in order to simulate a 'real-life'-like situation. DMARDs were used in all patients except two (3.6% of all patients), one of whom developed

TABLE 1. Initial DMARD treatment of the cohort. Subsequent switches were significantly more frequent in the erosive group (see text for details)

	Erosive	Non-erosive	<i>P</i>
Methotrexate	18 (51.4%)	3 (15%)	<0.001
Sulfasalazine	9 (25.7%)	8 (40%)	NS
Antimalarials	6 (17.1%)	6 (30%)	NS
Combination DMARDs	1 (2.8%)	1 (5%)	NS
Cyclophosphamide	0	1* (2.8%)	NS

*Because of co-existing demyelinating disease.

TABLE 2. Disease activity measures at baseline. Results are given as medians (IQR) because of non-normal distribution (all parameters NS, Mann–Whitney *U*-test). PGA (VAS), patients' global assessment of disease activity; PhGA, physicians' global assessment of disease activity

	Erosive	Non-erosive
Swollen joint count	6 (5, 12)	10 (5, 11)
Tender joint count	10 (4, 13)	12 (2.5, 20.5)
PGA (VAS)	53 (33, 68)	55 (34, 69)
PhGA (VAS)	45 (27, 58)	43 (35.5, 64.5)
HAQ	0.500 (0.000, 1.500)	1.250 (0.0625, 2.063)
ESR	52 (30, 78)	60.5 (21, 82)
CRP	1.8 (1.09, 5.0)	2.8 (1.3, 6.0)
RF titre	58 (12, 170.5)	0 (0, 0)
Anti-CCP titre	8 (0, 46.5)	0 (0, 0)

erosions during the observation period but had refused to take methotrexate as recommended. The time to start off the first DMARD was similar in patients who became erosive and non-erosive patients [median in both groups: 19 weeks after symptom onset, interquartile range (IQR) 4–24 (erosive), 4–30 (non-erosive)]. Remarkably, despite the fact that there were no significant differences in baseline characteristics (see subsequently), methotrexate as first DMARD was used more frequently in patients who later became erosive (Table 1).

During the 3 yrs observation period, initial DMARDs were replaced by one or more alternative DMARD treatments more frequently in the erosive patients (switch in 65.7%) than in the non-erosive group (switch in 20%, *P*<0.002). In the non-erosive group, only a single DMARD replacement took place in each of the four individuals who were switched. In the 23 patients in the erosive group, 2.1 (range: 1–6) DMARD changes took place over the 3 yrs period. Four patients (all in the erosive group) were started on tumour necrosis factor (TNF)- α antagonists after these became available in 2000.

Regarding the use of steroids, there was no statistically significant difference between the erosive and non-erosive patients in initial use (62.8% of the erosive patients *vs* 45% in the non-erosive group). 91 *vs* 70% received steroids at any time during the first 3 yrs (*P*=NS). Continuous use (steroids used on at least three consecutive visits during the observation period), however, was more frequent in the erosive patients (57 *vs* 25%, *P*=0.0268 by Fisher's exact test).

Core set variables and erosive disease in very early RA

In order to determine whether disease activity measures such as the internationally defined core set variables were associated with the development of erosions in patients with very early RA, we compared the values at presentation between the erosive and non-erosive patient groups. None of the clinical variables (numbers of swollen and tender joints, HAQ and patients' global assessment of activity of RA) was different between the two groups at baseline (Table 2).

We next analysed the core set parameters over the whole observation period by determining the average for each individual year. Although tender and swollen joints as well as all other measures decreased markedly over time in both groups, that decrease was numerically larger in patients who did not develop erosions. Interestingly, there was no statistically significant difference for any of the measures between the two groups at baseline and during the first year. However, during the second or the third year, the measures of disease activity, including joint counts, VAS, acute phase reactants and the DAS28, were statistically significantly higher in the erosive as compared with the non-erosive group (Fig. 3); similar results were obtained for the SDAI and the CDAI (data not shown).

Lasting clinical remission (as determined by a DAS28 below 2.6 for more than a year consecutively) was observed in 16 patients. Only five of these patients (31%) had erosive disease (two of them presented with erosions already at baseline, the other three developed erosions during the first year, after which they did not progress any further). Thus, longstanding remission (under treatment) was achieved in 29% of this early RA cohort and was associated significantly with the absence of erosive disease ($P=0.0022$ by Fisher's exact test).

Rheumatoid factor, anti-CCP antibodies, shared epitope and erosive disease

RF has been identified as a major risk factor for the development of erosions in RA [30]. This was the case also in the present cohort, representing patients with very early disease: in the group developing erosions, 22 patients (62.9%) were RF positive, whereas in the non-erosive patients, only two patients (10%) had a positive RF ($P<0.0002$). Among the 22 patients in the erosive group, 19 individuals had RF of >50 IU/ml, which is regarded as 'high titre' and was found associated with progressive radiological damage [31].

Regarding the presence of anti-CCP antibodies, a similarly strong association was found; presence of anti-CCP antibodies at baseline was highly predictive of development of erosions: there were 22 (62.9%) anti-CCP-positive patients in the erosive group and one (5%) anti-CCP positive patient in the non-erosive group, $P<0.0001$. Both antibodies (RF and anti-CCP) were found in 18 patients (51.4% of all erosive patients and $>80\%$ of each, the RF- and anti-CCP-positive groups, respectively).

Over the 3 yr observation period, despite DMARD (and steroid) treatment, titres of RF and anti-CCP remained very stable. We observed a small but non-significant decrease in median cumulative RF titres in the RF positive patients, in the anti-CCP positive patients, no change was apparent (data not shown).

Samples for determination of shared epitope genotypes were available from 44 patients (14 in the non-erosive and 30 in the erosive group). Genotypes DRB1*0101, *0102, *0401, *0404 or *1001 were present in 53.3% of the erosive as compared with 21.4% of the non-erosive group ($P=0.058$ by Fisher's exact test).

Core set parameters and radiological progression

In the non-erosive group, the change in modified Larsen scores from baseline after 3 yrs was zero by definition; within the erosive group, the difference in scores between the initial radiographs and the 3 yrs time point ranged from -4 (due to disappearance/healing of two small initial erosions in one patient after 3 yrs) to 75. Both anti-CCP- and RF-positive patients had highly significantly greater rates of progression than anti-CCP- and RF-negative individuals ($P<0.0001$ by Mann-Whitney U -test). In contrast, presence of the shared epitope genotype did not appear to significantly influence radiological score progression ($P=0.221$).

Most of the clinical and serological activity measures correlated statistically significantly with the radiological outcome. The strongest correlations were identified between progression in Larsen scores and time in low disease activity/remission (negative correlation), cumulative swollen or tender joint counts, cumulative patient global assessment by VAS, cumulative CRP and DAS28, respectively (Table 3). ESR and the cumulative HAQ correlated somewhat less strongly with radiological findings after 3 yrs. SDAI and CDAI gave similar findings (not shown).

Model for factors influencing radiological progression

On the basis of the latter analysis, a stepwise multiple regression model was derived: cumulative CRP, cumulative swollen joint count and total time in low disease activity and/or remission (DAS28-score <3.2) showed a significant contribution to the overall outcome after correcting for the presence of RF and anti-CCP (Table 4).

The model indicated that RF and anti-CCP determined 31.6% of the observed change in Larsen scores. An additional 30.5% of the total progression in Larsen scores can be attributed to the influence of the other three parameters (cumulative CRP, cumulative swollen joint count and total time in low disease activity and/or remission). Thus, the factors with the greatest increasing influence on the progression in Larsen scores were RF, anti-CCP, CRP and cumulative swollen joint count, while total time in low disease activity and/or remission had a decreasing effect on radiological progression, together explaining more than 60% of the radiological progression.

Discussion

Early treatment of RA has become a major paradigm in therapeutic strategies for RA. Despite relatively successful establishment of early arthritis clinics and ensuing (very) early initiation of DMARD treatment in a large proportion of early RA patients, radiographic progression in these patients is still substantial. Our cohort, which is continuously followed according to a standardized protocol, offers a unique opportunity to study the course of RA both clinically and radiologically in patients treated as soon as possible (mostly between 3 and 6 months after their first clinical symptoms).

In the present group of very early RA patients, 63.6% had erosive arthritis after 3 yrs. This appears relatively low when compared with the observation of others [7] and suggests that recognizing and treating potentially destructive arthritis as early as possible may prevent the occurrence of erosive disease at least in some patients. Importantly, clinical features of erosive and non-erosive patients such as joint counts, HAQ scores, VAS ratings as well as acute phase reactants did not differ at baseline, nor were the outcomes predictable by these clinical and laboratory criteria or their changes during the initial months of clinically manifest disease. In contrast, RF, especially at ≥ 50 U/ml, was able to discriminate early on between the two outcomes as well as to predict the pace of destruction over 3 yrs, and similar results were obtained with anti-CCP. The contribution of these two prognostic factors to the regression model for radiological progression amounts to approximately one-third. Since RF and anti-CCP are thought to even pre-date the first clinical manifestations of RA, and because they are believed to be surrogates of the complex underlying pathophysiological processes, the conclusion from these data may be that there is a subgroup of RA patients who are already determined to develop erosions even before the first clinical sign of arthritis. Interestingly, we did not find an influence of the shared epitope in our cohort. Although this conclusion should be taken with caution because of the relatively small number of patients analysed, it is in line with other recent observations [32].

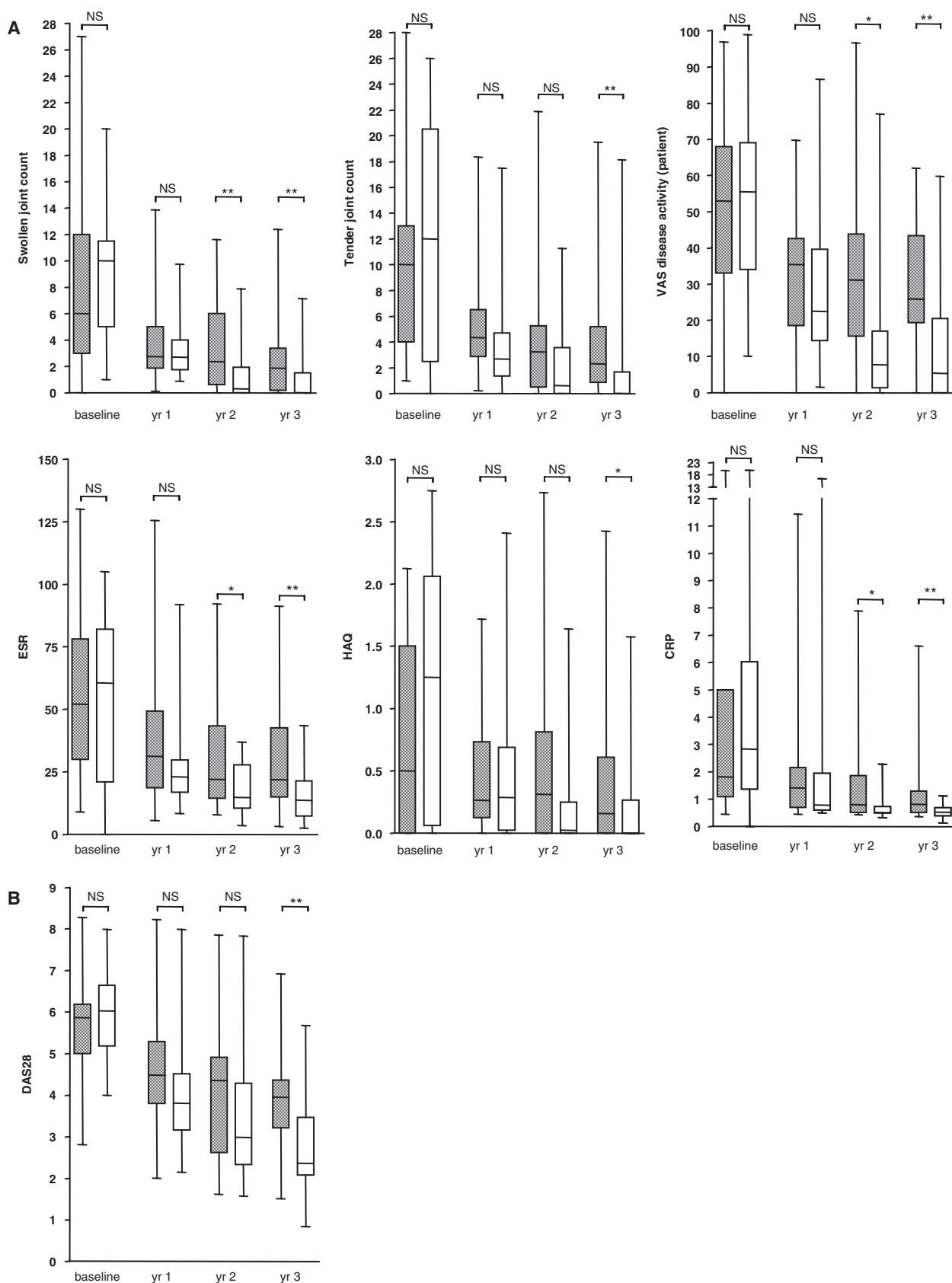


FIG. 3. Core set parameters over the whole observation period. Averages for each year were compared between erosive and non-erosive patients. Initially, none of the parameters was different between the erosive and non-erosive groups. Over the observation period, the erosive and non-erosive groups diverged, differing significantly with respect to all six measures. In addition, the DAS28 was significantly lower in the non-erosive group as compared to the erosive patients. [NS = $P > 0.05$, * $P < 0.05$, ** $P < 0.01$; Mann-Whitney U -test; open boxes: non-erosive patients, cross-hatched boxes: erosive patients. Boxplots represent medians, IQR, and range (whiskers)].

TABLE 3. Correlations between Larsen score progression and disease activity measures (PGA=patients global assessment of disease activity)

	Spearman correlation coefficient	P
Time in low disease activity/remission	−0.741	<0.0001
Cumulative swollen joint counts	0.584	<0.0001
Cumulative DAS28	0.543	<0.0001
Cumulative tender joint counts	0.454	<0.0001
Cumulative PGA (VAS)	0.443	0.001
Cumulative CRP	0.360	0.007
Cumulative ESR	0.346	0.01
Cumulative HAQ	0.303	0.025

TABLE 4. Stepwise multiple regression (controlled for RF and anti-CCP). 'Block 1' (RF and CCP) account for 34.2% of the progression in Larsen scores over three years, 'Block 2' (time in low disease activity, cumulative swollen joint count, cumulative CRP as a whole) contributes an additional 30.5% (bold type). Beta values (the individual variables' unique contributions) and their individual significance levels are given in italics

	Beta	Adjusted R ²	Change in R ²	P
Block 1:		0.316	0.342	<0.0001
RF	<i>0.321</i>		<i>0.050</i>	<i>0.055</i>
Anti-CCP	<i>0.314</i>			
Block 2:		0.609	0.305	<0.0001
Time in DAS28<3.2	<i>−0.387</i>		<i><0.0001</i>	
Cumulative swollen joint count	<i>0.264</i>		<i>0.012</i>	
Cumulative CRP	<i>0.187</i>		<i>0.048</i>	

In addition to the immunological variables, which do not change substantially over time, clinical measures which may vary greatly and which are thought to reflect disease activity had an overall similar impact on X-ray progression. Among them, the total time during which each patient fulfilled remission and/or low disease activity criteria and the extent of joint swelling (cumulative over time) made the most important contribution, while cumulative CRP was contributing substantially less. Regarding the DAS28, the data underline the usefulness of this composite parameter in monitoring disease activity. In addition, our analysis adds importance to the terms 'low disease activity' or 'remission', given the fact that patients who (most likely through treatment with DMARDs and/or steroids) achieved such a low disease activity state, and who remained in this state for extended periods of time during the first 3 yrs, suffered less damage than the rest. The observation that the cumulative swollen joint count (which in clinical routine is also frequently regarded as an important measure of activity and/or response) also is strongly associated with the degree of progression seems interesting. Replacing swollen joint counts by cumulative tender joint counts in our regression model would have yielded a similarly, although somewhat less strongly predictive model (data not shown). The fact that CRP and ESR had the least contribution in the model supports the observations that clinical assessment scores may be reliable enough to describe disease activity without relying on additional information from acute phase response variables [29].

Radiological damage followed a very inhomogeneous pace: a few patients, despite DMARD treatment, developed rapidly progressive destructions, reaching ~40% of maximum damage scores already after 3 yrs.

Consistent with the literature, the majority of the patients who had structural damage in their X-rays developed these

changes within the first 2 yrs [9, 33]. The present analysis, however, places the start of radiological destruction even further towards the initial periods of the disease, with over 70% of the erosive patients showing their first unequivocal signs of destruction already within 12 months after their first sign of arthritis, and (as reported previously) ~10% having eroded joints already at the first visit, <3 months after the first symptoms. In the present analysis, we show that a large part (~30%) of this progression may be explained by the presence of RF and anti-CCP antibodies.

One limitation of our study is that the number of patients in the cohort is relatively small. Thus, weaker associations between radiological damage and other factors (such as the genotype) [34, 35] may not have been detected. However, contributions of these factors, if any, are likely to be much smaller than the ones described in this report. The fact that 83 RA patients (60%) were unavailable for the analysis at year 3 is mainly due to the regional characteristic that the Vienna clinics serve a population of over 3 million inhabitants who have to travel up to 250 km to attend the clinics; moreover, in contrast to other countries, patients are free to choose and change clinics. Thus, they may prefer to be seen by their local practitioners or other rheumatologists in their vicinity after the initial assessments and therapeutic recommendations. Therefore, a certain 'allocation bias' (which is frequent in such settings) may have occurred. We are currently in the process of trying to follow these 'non-attender' patients. Interestingly, we found a higher proportion of patients who were treated with methotrexate as first DMARD in the group who developed erosions as compared with the non-erosive patients. None of the clinical or laboratory measures that were recorded, however, was significantly different initially between the two groups, including the proportion of RF positive patients. It is unlikely that methotrexate would predispose patients to developing erosions; likewise, it seems unlikely that higher clinical activity which is not reflected in the core set assessment may account for this difference. This observation thus would need to be confirmed in other cohorts in order to rule out a finding caused by chance or the mentioned 'allocation bias'.

During the initial years of recruitment of the present cohort, the new biological agents (especially TNF inhibitors), which are thought to be able to influence the destructive processes even more effectively than the 'conventional' DMARDs, were not available. Subsequently, several patients (all in the erosive group) were treated with these agents; however, given the overall small number of patients, the total number of biological therapies is too small to draw conclusions on the impact of these agents. However, given their impact on radiographic progression [36], the current data suggest that patients with adverse prognostic markers presented here should rapidly be switched to TNF-blocking agents, at least after an initial traditional DMARD has failed or even as first line (combination) therapy, as the recent data on TNF-blockers suggest [37–39]. Adapting therapy by intensive disease control as recently suggested [4, 40] would be fully in line with the observations of the present study.

Taken together, our observations in this cohort of patients, who were seen much earlier by a rheumatologist than most other patients with RA and in whom (DMARD or steroid) treatment was in general started 3–6 months after the first disease manifestation, show, that despite this early treatment substantial damage may occur in some and that this damage is associated with (i) presence of strong immuno-inflammatory predictors such as RF, CRP, and anti-CCP and (ii) the persistent presence of clinical indicators of high disease activity such as, swollen (or tender) joint counts and absence of a good clinical response (assessed by the failure to achieve lasting low disease activity according to established composite disease activity indices).

Rheumatology	Key messages
	<ul style="list-style-type: none"> Joint damage in RA occurs despite very early treatment—visible often after only 12 months. RF, anti-CCP, persistent swelling and failure to achieve lasting good response determine radiological progression.

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