RHEUMATOLOGY

Concise report

The long-term impact of early treatment of rheumatoid arthritis on radiographic progression: a population-based cohort study

Diego Kyburz[1], Cem Gabay[2], Beat A. Michel[1] and Axel Finckh[2] for the physicians of the SCQM-RA[3]

Abstract

Objective. To measure the long-term rate of radiographic progression in a cohort of patients treated early *vs* late with conventional DMARDs.

Methods. The long-term rate of radiographic progression in patients included in the Swiss clinical quality management in rheumatoid arthritis (SCQM-RA) registry who initiated treatment with conventional DMARDs within the first year of symptom onset (early DMARD) *vs* patients who initiated treatment 1–5 years after symptom onset (late DMARD). Radiographic progression was assessed in 38 joints using a validated score (Ratingen Score). The rate of progression was calculated using a multivariate regression model for longitudinal data, adjusting for potential confounders.

Results. A total of 970 RA patients were included. The 368 patients in the early DMARD group started therapy after a median symptom duration of 6 months, whereas the 602 patients in the late DMARD group initiated therapy after median 2.5 years. RF, MTX use and other risk factors for erosive disease progression were similar between the two groups. However, the estimated rate of radiographic progression at baseline was higher in the early DMARD *vs* the late DMARD group (1.8 *vs* 0.6, $P < 0.01$). In spite of this, the long-term rate of radiographic progression was significantly lower in the early DMARD group after adjustment for confounding factors (-0.35 at 5 years, $P = 0.012$).

Conclusion. This result supports the concept of a therapeutic window of opportunity early in the disease course and suggests that early initiation of DMARD therapy results in a long-lasting reduction of radiographic damage.

Key words: Rheumatoid arthritis, Anti-rheumatic therapy, Radiographic progression, Disease-modifying anti-rheumatic drug, Cohort, Swiss clinical quality management in rheumatoid arthritis, Therapeutic window.

CLINICAL SCIENCE

Introduction

RA is a chronic autoimmune disease characterized by chronic inflammation and destructive changes of the joints, resulting ultimately in physical disability. Treatment is based on drugs that reduce inflammation and slow the progression of joint damage, the so-called DMARDs.

Seminal studies have shown that early initiation of DMARD treatment can have a lasting benefit [1–3]. Whereas several trials have established the short-term benefits of early initiation of DMARD treatment, the data on the long-term effects on the disease course are somewhat controversial. Some studies demonstrated persistent effects on radiographic progression, others did not [2, 4–7]. A recent meta-analysis of the literature showed that the long-term rates of radiographic progression were significantly lower in patients starting DMARDs early as compared with patients starting later [8]. However, no randomized controlled trial comparing early *vs* late therapy with similar DMARD regimens have been performed. In this study, we analysed the rates of long-term radiographic progression in a large patient cohort with regard to the latency between symptom onset and DMARD initiation.

[1]Department of Rheumatology, University Hospital of Zurich, Zurich, [2]Division of Rheumatology, University Hospitals of Geneva, Geneva and [3]SCQM Foundation, Zurich, Switzerland.

Correspondence to: Diego Kyburz, Department of Rheumatology, University Hospital of Zurich, Gloriastrasse 25, 8091 Zurich, Switzerland. E-mail: diego.kyburz@usz.ch

Patients and methods

Study design

This is a longitudinal, observational, population-based cohort study nested within the Swiss Clinical Quality Management for Rheumatoid Arthritis (SCQM-RA) registry.

Study population

The SCQM-RA registry is a longitudinal cohort of RA patients, which has been described in detail elsewhere [9]. Inclusion criteria for this study were a diagnosis of RA established by a board-certified rheumatologist, enrolment in the SCQM-RA within 5 years of symptom onset, simultaneous initiation of a DMARD therapy and availability of sequential radiographs since enrolment. Exclusion criteria were the absence of DMARD therapy during the first 5 years of symptom onset. We further excluded from the primary analysis patients who started their anti-rheumatic therapy with a biologic agent, because we felt that these patients represent a subgroup with very severe disease, not representative of the overall RA population. We included all patients of the database corresponding to these inclusion and exclusion criteria between January 1997 and December 2008. Ethical approval for the collection of patient data for the SCQM register was given by the regional review boards. Informed consent was obtained from all patients before inclusion into the SCQM register.

Outcome of interest

This study's primary end point was radiographic disease progression as measured by change from baseline in radiographic damage scores. We used a validated scoring method to assess the number and size of juxta-articular bone erosions (Ratingen Score) [10], which is sensitive to change and appears less susceptible to ceiling effects in advanced disease [11].

Exposure of interest and predictors

The exposure of interest for this study was the latency between symptom onset and DMARD initiation. We purposefully decided to use the notion of symptom onset as defined by the patient instead of disease onset defined by the physician, because in most patients RA symptoms precede the diagnosis by several months or years. We felt that latency between symptom onset and DMARD initiation probably better characterizes the notion of therapeutic window of opportunity than latency between diagnosis and DMARD initiation, commonly used in randomized trials. We dichotomized the time delay between symptom onset and DMARD initiation and arbitrarily defined two groups:

- early DMARD: if conventional DMARDs were initiated within 1 year of symptom onset; and
- late DMARD: if conventional DMARDs were initiated between 1 and 5 years of symptom onset.

Conventional DMARDs were defined as MTX, LEF, SSZ or other conventional DMARDs (HCQ, parenteral Gold, ciclosporin). We excluded glucocorticoid monotherapy from this definition, as glucocorticoid monotherapy tends to be given to patients with milder forms of the disease. Important predictors of RA disease progression such as measures of disease activity, self-assessed symptom questionnaires, various disease characteristics, demographic characteristics and treatment information were extracted from the database to be used in the analysis. Another predictor was the estimated yearly rates of radiographic progression at baseline, which was computed by dividing the radiographic scores at baseline by the disease duration [12]. We determined the time span in years for which each individual DMARD regimen had been used during follow-up and used this variable to control the analysis for DMARD use. Disease characteristics and other covariates were extracted from the SCQM-RA database. For sporadically missing covariates, which never exceeded 5% of any given covariate, we used population means.

Statistical analysis

Baseline disease characteristics were compared between two groups using adequate descriptive statistics. All statistical tests were two-sided and evaluated at the 0.05 significance level. The statistical analysis was performed with Stata version 9.2 for Windows (Stata Statistical Software, College Station, TX, USA).

The relationship between delay in DMARD initiation and radiographic progression could potentially be confounded by differences in disease characteristics and in treatments. We therefore used multivariate longitudinal regression and adjusted for potential confounding factors [13]. RF, baseline disease activity [28-joint DAS (DAS-28)], baseline functional disability (HAQ), baseline estimated rates of radiographic damage progression, age, sex, socio-economic status (educational level) and co-therapy with MTX, LEF, SSZ, other DMARDs, no DMARDs or glucocorticoids were considered confounders *a priori* and forced into the model. We further explored effect modification by RF positivity, concomitant glucocorticoids, concomitant MTX and estimated baseline radiographic progression. Patients who started their DMARD therapy straight with a biological agent were excluded. However, a sensitivity analysis with these patients was performed, comparing early biologic *vs* late biologic initiation.

Results

A total of 970 patients corresponding to the study criteria could be included. The average follow-up time was 4 years, with a median of three sequential X-rays of hand and feet. Within 1 year of symptom onset, 368 patients were started on DMARD treatment, with a median time of 6 months. In the late DMARD group, therapy was initiated after a median time of 2.3 years (range 1–5 years). At baseline, no significant differences between the two groups were noted for age, sex, RF-positivity and

TABLE 1 Baseline characteristics of patients treated early versus late with DMARDs

Baseline disease characteristics	Early DMARD (*n* = 368)	Late DMARD (*n* = 602)	*P*-value
Symptom duration, median, years	0.5	2.3	a
Female sex, *n* (%)	71	73	0.41
Age, mean, years	55	54	0.15
RF$^+$, *n* (%)	64	68	0.19
ERO at inclusion,[a] median	0.9	1.4	<0.01
Estimated baseline rate of ERO progression[a]	1.8	0.6	<0.01
Disease activity (DAS-28), median	4.7	4.1	<0.01
Functional disability (HAQ), median	1	0.8	0.04
Educational level, median, years	12	12	0.18
First DMARD (≥1 drug allowed), *n* (%)			
MTX,	83	80	0.27
LEF	7	16	<0.01
SSZ	14	19	0.02
HCQ	9	16	<0.01
Combination DMARDs	11	26	<0.01
Concomitant glucocorticoid use, *n* (%)	65	49	<0.01

[a]ERO and ERO progression (median) are indicated as the percentage of the maximum Ratingen score. The population averages are expressed in means, if not indicated otherwise.

educational level (Table 1). Disease activity was significantly higher in the early DMARD group at baseline, consistent with a higher estimated rate of radiographic progression at baseline in this group. MTX was the most commonly prescribed first DMARD (>80%) and it was prescribed with the same frequency in both groups. Significantly more patients in the late DMARD group were on LEF and HCQ, reflecting a higher percentage of patients receiving combination DMARD treatment in the late DMARD group. On the other hand, significantly more patients in the early group were treated with concomitant glucocorticoids (65 *vs* 49%). As expected, the erosion score (ERO, Ratingen score) at baseline was significantly higher in the late DMARD group compared with the early DMARD group (median 1.4 *vs* 0.9, *P* < 0.01). However, the estimated rate of ERO progression at baseline was higher in the early DMARD group, suggesting that the early DMARD group had a more severe disease.

The primary outcome was radiographic joint damage progression as measured by the change in Ratingen score. The unadjusted slopes of radiographic progression differed between the two groups (*P* = 0.012), with less damage progression in the early DMARD group. When the results were adjusted for potential confounding factors, radiographic progression in the early DMARD group remained significantly lower compared with the late DMARD group (*P* < 0.001, Fig. 1). Four years after symptom onset, the mean radiographic progression was 0.31%/year (95% CI 0.49, 0.13) higher in the late DMARD group compared with the early group. The beneficial effect of early DMARD treatment was significantly higher in patients with high levels of estimated radiographic progression at baseline [additional decrease in long-term damage progression by −0.19%/year (95% CI −0.26, −0.12); *P* < 0.0001 in the highest quartile]. Neither

FIG. 1 Progression of ERO (Ratingen score) over time in early *vs* late DMARD-treated patients. Mean EROs (s.e.m.) are shown as percentages of maximum damage score as a function of time since symptom onset. Regression analysis with adjustment for risk factors for radiographic progression revealed a significant difference in the slopes of the two curves.
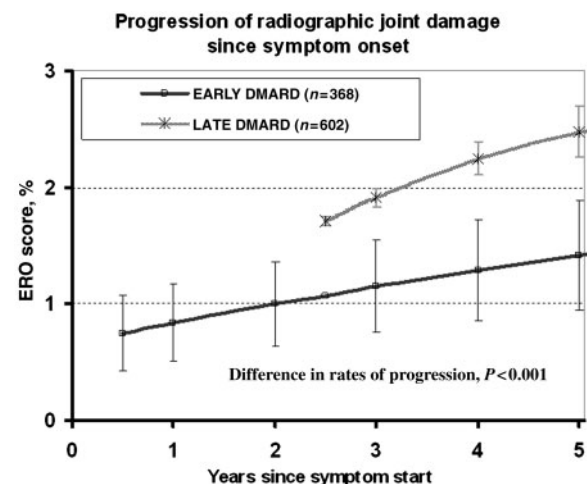
RF positivity nor co-medication with glucocorticoids modified significantly the effect of early DMARD treatment. However, patients treated with glucocorticoids tended to have more rapid radiographic progression than patients not receiving glucocorticoids. This probably reflects the fact that concomitant glucocorticoid therapy is an indicator of severe disease. Treatment with MTX as opposed to other conventional DMARDs did not modify the

relationship between early DMARD and late DMARD, suggesting that the type of DMARD treatment was not decisive for the outcome. An exploratory analysis of patients starting their anti-rheumatic treatment with a biologic agent revealed similar trends for long-term reduction of radiologic progression in the early treatment group (data not shown).

Discussion

In this cohort study, we found a significantly lower progression rate in RA patients treated early with DMARDs compared with later, which was not explained by differences in anti-rheumatic treatment regimen or other differences in disease characteristics. The benefit of early DMARD intervention was significantly greater in patients with high radiographic progression at baseline. Our data suggest that early DMARD treatment offers a long-term benefit on joint damage progression and supports the concept of a therapeutic window of opportunity early in disease.

A large meta-analysis of 1435 patients suggested that disease duration at the start of DMARD treatment was the main predictor of a clinical response to therapy [14]. While the short-term benefit of early DMARD treatment is well established, only few studies have shown a benefit of early therapy on long-term radiographic progression and no randomized trial has compared early *vs* late treatment with a similar DMARD regimen. The present analysis confirms similar findings in smaller follow-up studies [4–5]. In spite of a higher estimated rate of radiographic progression at baseline, the early DMARD cohort had a significantly lower progression rate over 5 years compared with the late DMARD group. This difference was also not explained by variations in anti-rheumatic therapy, as there were no substantial differences in DMARD use between the groups and >80% of patients in both groups were treated with MTX. In an exploratory analysis, we examined only patients treated with MTX and found a similar trend, with no evidence for effect modification by the type of conventional DMARD. Overall 22% of the patients eventually started anti-TNF agents over time and the proportion of anti-TNF initiation was similar in the early and late DMARD groups ($P = 0.91$). Also, there were no differences in seropositivity with RF between the groups, but we missed anti-CCP status for a majority of patients.

The absolute radiographic damage at 5 years was significantly lower in the early treatment group despite the fact that the estimated progression rate at baseline was higher in this group. To explain the differences in radiographic progression, it can be hypothesized that early suppression of inflammatory processes in the joint may prevent irreversible steps of the disease pathogenesis. Several clinical studies have shown that early aggressive therapy of RA can result in long-term remission [15], sometimes even DMARD-free remission [16], suggesting that the disease pathogenesis has been profoundly modified, resulting in long-term remission and suppression of radiological progression.

This analysis has potential limitations inherent to the analysis of observational data. In this study, there was no control over the treatment assignment of early DMARD *vs* late DMARD. Because the most frequent reason for delayed DMARD initiation is deferred referral to a rheumatologist [17], substantial confounding by indication between early and late DMARD is unlikely. Confounding by indication would most likely bias the results towards the null, since the most severely affected patients are likely to consult earlier and be in the early DMARD group. This was suggested by a higher level of estimated baseline radiographic progression in the early DMARD group and higher use of concomitant glucocorticoids. While we could adjust our analysis for many important disease characteristics potentially associated with radiographic progression, we cannot exclude the possibility of confounding by unmeasured factors. Strengths of this analysis include a population-based cohort, a systematic prospective ascertainment of a wide variety of potential confounders and longitudinal radiographical data.

In conclusion, we show in a large patient population with RA that the radiographic progression over 5 years is significantly lower in patients with early initiation of DMARD treatment. Our data provide confirmatory evidence of a long-lasting effect of early disease control, supporting the existence of a therapeutic window of opportunity early in the development of RA.

> **Rheumatology key message**
> - Early DMARD treatment results in long-lasting decrease of radiographic progression rate.

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