Estimated Pre-diagnosis Radiological Progression: an important tool for studying the effects of early DMARD-therapy in rheumatoid arthritis

CONCISE REPORT

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Abstract

Objective: To determine if intra-patient comparisons between pre-diagnosis and subsequent radiological progression could be used to assess the effects of DMARDs in a RA-inception cohort.

Patients and Methods: We analyzed 149 non-randomized newly diagnosed RA patients. Four groups were chosen: 1) patients treated with methotrexate (MTX, n=56), 2) sulfasalazine (SSZ, n=55), 3) and auranofin (AUR, n=19), and 4) a control-group of patients who changed therapy at least twice, representing poor therapy-responders with persistent clinical activity (control, n=19). Radiographs were quantified using Larsen erosion score. Taking the first onset of RA-symptoms as the earliest starting date for radiological damage, the pre-diagnosis rate of radiological progression was calculated and compared to the observed progression rate during the first year after diagnosis while under DMARD-therapy.

Results: The mean disease duration in all patients from onset of symptoms until diagnosis of RA and DMARD-institution was 6.7±4.0 months. The mean baseline Larsen score was 13.2±9.3, resulting in a mean estimated pre-diagnosis progression rate of 23.6±12.4 Larsen score units/year. In the control- and AUR-group, radiological progression after diagnosis was similar to the progression predicted by the pre-diagnosis progression rates. In the patients for whom MTX or SSZ was the first-line therapy, a marked reduction (71% and 73% respectively; p<0.001) in radiographic progression was seen compared to pre-diagnosis progression.

Conclusions: Pre-diagnosis rates of radiological progression can be used quantitatively to obtain important information on the potential efficacy of DMARDs, and indicate that MTX and SSZ, but not AUR, significantly retard radiographic damage in the first year after diagnosis.
Introduction

Radiological damage is an important outcome measure in rheumatoid arthritis (RA) (1) and correlates well with functional outcome (2). It has been suggested that estimates of yearly progression of radiological damage, obtained by dividing changes in x-ray scores by time, can reliably be used for numerical comparisons between different treatments (3).

While current recommendations favour aggressive DMARD-therapy for early RA in order to prevent or slow radiological damage, recent studies have indicated that early DMARD-therapy does not completely prevent radiographic progression even in the first year after diagnosis of RA (4;5). Thus, an important question is whether early DMARD-therapy changes the rate of radiological progression. We investigated this question by assuming that radiographic damage commences at the onset of RA symptoms, making it possible to calculate the rate of untreated radiographic progression prior to diagnosis, and compare this rate to the observed rate of progression during the first year after diagnosis, during which period the patients were given DMARD-therapy.

The aim of this study was to analyze the feasibility of this new method and using this method to determine if the most commonly used DMARDs in our longitudinal early RA-inception cohort reduced radiographic progression. Our data show that pre-diagnosis radiological progression can successfully be used in this manner, and suggest that methotrexate and sulfasalazine, but not auranofin, retard radiological progression in the first year of RA.
Patients and Methods

We evaluated clinical data and radiographs of 149 early RA patients registered in the Swedish Rheumatoid Arthritis Registry. Although the Swedish Rheumatoid Arthritis Registry is a collaborative effort of many Swedish Rheumatology units, the data presented herein are based on patients treated in our unit at the Karolinska Hospital. Eligibility for inclusion in this study required that patients: (i) were diagnosed with RA, (ii) evaluated clinically within the first year after onset of symptoms, (iii) commenced DMARD-therapy within two months after their first presentation to our early-arthritis clinic, (iv) underwent at least one year of follow-up to document laboratory and clinical values, (vi) had at least two sets of radiographs of hands and feet taken at baseline and during follow-up, with the interval between the two sets of x-rays not exceeding one year, and (vii) were treated with methotrexate (MTX, n=56), sulfasalazine (SSZ, n=55), or oral gold (AUR, n=19), or, as a control-group, we included patients who, because of poor clinical responses, changed therapy at least twice during the first two years after diagnosis and whom we previously showed (6) to represent a group of poor therapy-responders with persistent clinical activity (control, n=19). DMARDs were generally administered as follows: AUR at 6 mg/day; MTX at 7.5-15 mg/week; SSZ at 2 g/day.

Measurements: The following clinical parameters were determined at baseline, 3, 6, 9, and 12 months after diagnosis: Erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), ACR 28 tender and swollen joint counts (TJC, SJC), patients global assessment (0-10 cm VA-scales), pain (0-10 cm VA-scales), health assessment questionnaire (HAQ), and the disease activity score DAS28 (7).

Radiographs: Identical radiographs of the hands and feet were taken of all patients in posterior-anterior and tangential views at baseline and at one year follow-up. Radiographs were assessed after achieving satisfactory intraobserver reliability (0.93-0.95). The radiographs were scored blinded to treatment, in pairs (hands and feet), and in chronological
sequence applying the Larsen method (8). The scoring procedure was performed and
documented by an experienced investigator (MCW) using the computer-assisted
quantification software “X-Ray RheumaCoach” (9). In each case, thirty-two joints were
scored: 8 proximal interphalangeal, 2 thumb interphalangeal, 10 metacarpophalangeal, 2
wrists, 2 hallux interphalangeal, and 8 metatarsophalangeal joints (II-V). Each wrist was
scored as a unit and multiplied by 5.

The aggregate Larsen score was modified slightly by excluding grade 1, so that the scale
became 0-4 (grades 1 and 0 were combined and designated grade 0, grade 2 was called grade
1, grade 3 was called grade 2, grade 4 was called grade 3, and grade 5 was called grade 4)
(10). Thus, the maximum possible score was 160. \( \Delta \text{Larsen score} \) was calculated by
subtracting baseline Larsen score values from the respective annual score. The rate of
radiological progression per time was calculated, taking the first onset of RA-symptoms as the
initiation of pre-diagnosis radiographic destruction.

Statistical analysis: All data are given as means±SD. Statistical comparisons were performed
using analyses of variance followed by post hoc Bonferroni’s test, and Student’s t-test. All
statistical analyses were performed using SPSS\textsuperscript{\textregistered} 11.5 for Windows\textsuperscript{\textregistered} (SPSS Inc., Chicago, IL).
Results

Table 1 summarizes the demographic, clinical, and radiological baseline values and 1-year follow-up data of the 149 patients included in this analysis. Of note, this was not a randomized trial, since the choice of treatment was based on individual patient clinical considerations. Thus, these patients represented a “real-life”-sample of early RA patients at our early-arthritis center. Differences between the groups were seen for some baseline values (Table 1). The mean age at RA-diagnosis and institution of treatment was 57.5±15.3 years. The mean time from onset of symptoms (as recorded by the patient) until diagnosis of RA was 6.7±4.0 months. None of the patients received any DMARD-treatment prior to diagnosis. Clinical outcomes such as TJC, SJC, and the DAS28 improved from baseline to year 1 under DMARD-therapy, but not in the control-group (Table 1). The mean baseline Larsen score was 13.2±9.3 (mean±SD; median 12, IQR 5.8-18.5) and increased to 20.5±10.8 (median 20, IQR 11.0-29.0) during one year of treatment, i.e., the mean increase in radiographic damage from baseline to year 1 was 7.9±6.0.

Taking the first onset of RA-symptoms as the earliest possible commencement of radiological destruction, the radiological progression rate up to the time of diagnosis was calculated. For all 149 patient, the rate was 23.6±12.4 Larsen score units/year and for the 4 groups the pre-diagnosis progression rate varied from 16.6±11.5 to 27.4±16.5 (Table 2). When comparing the estimated pre-diagnosis progression rate to the progression occurring during year 1 following diagnosis (Fig. 1), an attenuation of the progression rate was seen in all groups. However, the reduction in radiographic progression rate in the MTX and SSZ groups was much greater and statistically significant (reductions of 71% and 73% respectively; p<0.001 either treatment when compared to predicted progression) whereas the reductions in radiographic progression rate were smaller and not statistically significant in the AUR and control-patient groups (43% and 41% respectively) (Table 2). The decreases in progression-rate were statistically different between the 4 groups by ANOVA (p<0.05).
Discussion

We wished to employ an important and in some aspects new method of comparing radiological progression prior to diagnosis with progression observed during the first year after diagnosis in order to study the effects of early intervention with DMARDs. The method in this study is not to be confused with the recently described method of estimating radiological progression prior to inclusion in a clinical trial in patients with long-standing RA (11).

The results presented herein demonstrate the feasibility of this approach and suggest that administration of MTX or SSZ, but not AUR, significantly attenuates the destructive course of this disease already in the first year after diagnosis.

Recent emphasis on early intervention complicates identification of appropriate control-groups in longitudinal studies designed to evaluate various therapeutic regimens. The control-group included in this study was defined as RA patients who were considered to be “poor clinical responders”, and who underwent changes in DMARD-treatment at least twice during the first two years after their initial diagnosis. During follow-up, these patients showed no perceptible improvement in clinical disease activity indices, making them a useful control-group for comparisons in a longitudinal database, and indeed, compared to MTX, SSZ, and AUR, control-patients showed the greatest increase of radiographic score from baseline to year 1. The number of patients in the AUR and control groups were relatively small for a long-term observational study, putting a limitation on the generalizability of our results.

We used the time of onset of RA-symptoms as the earliest initiation of radiological destruction to estimate pre-diagnosis progression-rates. Hypothetically, the first radiological damage could have preceded the earliest reported symptoms, but then the data would suggest that radiographic progression increased after the institution of DMARD-treatment, which is less likely. Conversely, it is also possible that radiological progression starts after the first clinical symptoms become apparent. In this case, our results suggest even more convincingly
that early intervention with MTX and SSZ retards radiological damage compared to AUR-treated or non-responder controls. It needs to be mentioned, however, that estimation of pre-diagnosis radiological progression in patients with very short duration of symptoms may sometimes be overestimates.

In conclusion, estimates of pre-diagnosis radiographic progression can be used quantitatively to assess the potential therapeutic efficacy of DMARDs in early RA, and suggest that both MTX and SSZ, but not AUR, significantly retard radiographic damage in the first year after diagnosis. Pre-diagnosis rates of radiological progression can be an important tool for assessing the benefit of early, aggressive treatment in RA.
References


### Tables

<table>
<thead>
<tr>
<th>Treatment</th>
<th>MTX (n=56)</th>
<th>SSZ (n=55)</th>
<th>AUR (n=19)</th>
<th>control (n=19)</th>
<th>p*</th>
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<tr>
<td><strong>Demographic Characteristics</strong></td>
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<tr>
<td>Age ± SD (years)</td>
<td>63.4 ± 13.0</td>
<td>53.6 ± 15.9</td>
<td>59.1 ± 13.1</td>
<td>50.2 ± 16.3</td>
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<td>Males</td>
<td>16 (29%)</td>
<td>24 (43.6%)</td>
<td>7 (36.8%)</td>
<td>4 (21.05%)</td>
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<td>Females</td>
<td>40 (71%)</td>
<td>31 (56.4%)</td>
<td>12 (63.2%)</td>
<td>15 (78.95%)</td>
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<tr>
<td>Disease duration (months)</td>
<td>6.8 ± 3.9</td>
<td>6.5 ± 3.6</td>
<td>7.0 ± 4.4</td>
<td>6.5 ± 4.2</td>
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<td><strong>Clinical Baseline Values</strong></td>
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</tr>
<tr>
<td>ESR (mm/h)</td>
<td>29.5 ± 20.3</td>
<td>28.2 ± 23.1</td>
<td>16.3 ± 9.6</td>
<td>29.9 ± 21.9</td>
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<td>CRP (mg/dl)</td>
<td>3.2 ± 4.0</td>
<td>1.9 ± 1.8</td>
<td>1.1 ± 0.9</td>
<td>2.9 ± 3.2</td>
<td>0.03</td>
</tr>
<tr>
<td>DAS28</td>
<td>5.4 ± 1.1</td>
<td>4.8 ± 1.1</td>
<td>4.1 ± 0.9</td>
<td>5.0 ± 1.0</td>
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<td>HAQ</td>
<td>1.1 ± 0.6</td>
<td>0.8 ± 0.5</td>
<td>0.8 ± 0.5</td>
<td>1.1 ± 0.6</td>
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<td>SJC</td>
<td>11.0 ± 5.6</td>
<td>10.3 ± 5.8</td>
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<td>7.6 ± 5.4</td>
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<td>TJC</td>
<td>9.8 ± 6.2</td>
<td>7.5 ± 6.0</td>
<td>4.6 ± 3.7</td>
<td>7.2 ± 5.5</td>
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<tr>
<td>Pain</td>
<td>4.8 ± 2.3</td>
<td>3.7 ± 2.1</td>
<td>3.9 ± 2.5</td>
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<td>Patients assessment</td>
<td>4.5 ± 2.4</td>
<td>3.7 ± 2.5</td>
<td>4.4 ± 2.4</td>
<td>5.6 ± 2.7</td>
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<td>Larsen score</td>
<td>15.6 ± 9.6</td>
<td>12.9 ± 9.4</td>
<td>9.6 ± 7.0</td>
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<td><strong>Clinical Values after 1 Year of Therapy</strong></td>
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<tr>
<td>ESR (mm/h)</td>
<td>19.5 ± 16.8</td>
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<td>12.3 ± 9.2</td>
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<td>CRP (mg/dl)</td>
<td>1.7 ± 2.6</td>
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<td>0.9 ± 0.7</td>
<td>1.9 ± 2.3</td>
<td>0.001</td>
</tr>
<tr>
<td>DAS28</td>
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<td>3.2 ± 1.5</td>
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<td>0.001</td>
</tr>
<tr>
<td>HAQ</td>
<td>0.8 ± 0.5</td>
<td>0.5 ± 0.5</td>
<td>0.7 ± 0.5</td>
<td>1.0 ± 0.6</td>
<td>0.001</td>
</tr>
<tr>
<td>SJC</td>
<td>4.8 ± 5.4</td>
<td>4.0 ± 5.0</td>
<td>2.3 ± 2.9</td>
<td>5.0 ± 4.6</td>
<td>0.001</td>
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<td>TJC</td>
<td>4.6 ± 5.3</td>
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<td>0.001</td>
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<tr>
<td>Pain</td>
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<td>2.8 ± 2.4</td>
<td>3.1 ± 2.2</td>
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<tr>
<td>Patients assessment</td>
<td>3.5 ± 2.4</td>
<td>2.8 ± 2.3</td>
<td>3.3 ± 2.4</td>
<td>4.5 ± 2.6</td>
<td>0.001</td>
</tr>
<tr>
<td>Larsen score</td>
<td>23.2 ± 11.3</td>
<td>18.9 ± 12.6</td>
<td>18.9 ± 9.8</td>
<td>20.0 ± 8.5</td>
<td>0.2</td>
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</table>

Table 1 Baseline Characteristics and values after one year of therapy in patients with early RA; # Based on a 28-joint count; § estimated by visual analogous scale (VAS 0-10cm); *ANOV followed by post hoc Bonferroni's test.
<table>
<thead>
<tr>
<th>Treatment</th>
<th>MTX (n=56)</th>
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<th>AUR (n=19)</th>
<th>control (n=19)</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-diagnosis progression rate (change/year)</td>
<td>27.4±16.5</td>
<td>23.8±16.9</td>
<td>16.6±11.5</td>
<td>17.6±13.6</td>
<td>0.1</td>
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<tr>
<td>Progression from Baseline to year 1</td>
<td>7.9±4.6</td>
<td>6.5±4.9</td>
<td>9.4±6.8</td>
<td>10.4±4.9</td>
<td>0.025</td>
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<tr>
<td>Decrease in rate of progression</td>
<td>-19.5±9.3</td>
<td>-17.3±10.2</td>
<td>-7.2±4.4</td>
<td>-7.2±4.8</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Table 2. Estimated rates of radiological progression prior to diagnosis (and institution of DMARD-treatment) and Δ Larsen scores during year 1 (Larsen score units/year±SD); the pre-diagnosis radiological progression rate was estimated by dividing radiological damage at baseline by symptom duration as recorded at the baseline visit for each patient; *comparison of 4 groups by ANOVA; †comparison of pre-diagnosis progression vs. progression from baseline to year 1, for each group (paired Student’s t-test).
Figure legends

Fig. 1: Increment of Larsen score in the four different treatment groups MTX (1a), SSZ (1b), AUR (1c), and controls (1d); shown are means±SD. Pre-diagnosis radiological progression is represented as a straight line starting at the time of symptom onset. Estimated progression from baseline to year 1 is represented as a dotted line extending from the pre-diagnosis radiological progression. Actual observed radiological progression is represented as an unbroken line.
A = Onset of RA symptoms

- MTX
- SSZ
- AUR
- control

1a: MTX vs control

1b: SSZ vs control

1c: AUR vs control

1d: MTX vs SSZ vs AUR vs control

p<0.001
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