

# Frequency of Remissions in Early Rheumatoid Arthritis Defined by 3 Sets of Criteria. A 5-Year Followup Study

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**ABSTRACT. Objective.** To study the frequency of remission using 3 sets of criteria in patients with rheumatoid arthritis (RA) at 5 years after the diagnosis.

**Methods.** All adult patients with recent onset inflammatory arthritis who did not meet criteria or show clinical signs of other specific arthritides were included in the RA1997 inception cohort at Jyväskylä Central Hospital, Finland, and were assessed for remission at 5-year control examination. Remission was defined as (1) American College of Rheumatology (ACR) remission (fatigue excluded), (2) clinical remission with no tender and no swollen joints and normal erythrocyte sedimentation rate, and (3) radiographic remission with no worsening of erosions and no new erosions from baseline to 5 years.

**Results.** The study included 127 patients with early RA (mean age 56 yrs, 61% female, 54% with positive rheumatoid factor, and 25% with erosions). At 5 years, 111 patients were examined, 17% (95% CI 11%–25%) of whom met ACR remission criteria, 37% (95% CI 28%–47%) met clinical remission criteria, and 55% (95% CI 49%–68%) met radiographic remission criteria. Only 13 (12%) patients met all 3 sets of remission criteria. The rate of remission was statistically significantly different ( $p < 0.001$ ) using the 3 sets.

**Conclusion.** The rate of remission in RA depends on the criteria used. No gold standard exists for defining remission in RA. A set of criteria including no sign of inflammatory activity and no radiographic progression might be a basis for development of clinically relevant remission criteria for RA. (J Rheumatol 2005;32:796–800)

*Key Indexing Terms:*

REMISSION

RHEUMATOID ARTHRITIS

EARLY RHEUMATOID ARTHRITIS

Rheumatoid arthritis (RA) is a disease with unpredictable outcome, often with serious consequences to the patient and to society<sup>1</sup>. However, disease prognosis varies considerably. Clinical remission is the most desirable outcome.

Various definitions of remission have been used in the literature. Preliminary remission criteria for RA proposed in 1981 by Pinals, *et al*<sup>2</sup> were adopted by the American College of Rheumatology (ACR). Other, less rigorous definitions such as “being symptom-free” or “no arthritis on examination” have also been used<sup>3–6</sup>. Radiographic remission refers to no progression of radiographic damage<sup>7</sup>. Remission can either be referred to a single time point or the requirement of duration can be included in the criteria.

Permanent remission in RA is rare. Depending on the criteria applied, the population studied, and the therapy given, the rate of remission over 1–10 years after RA diagnosis can vary from 0% to 42%<sup>4–6,8–18</sup>.

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We explored the frequency of remission at 5 years in an inception cohort of patients with early RA using 3 sets of remission criteria: ACR remission criteria<sup>2</sup>; clinical remission with no tender and no swollen joints and normal erythrocyte sedimentation rate (ESR); and radiographic remission criteria with no new erosions and no worsening of erosions after baseline<sup>7</sup>.

## MATERIALS AND METHODS

**Study population.** Jyväskylä Central Hospital, the only rheumatology center in the Central Finland District, serves a population of 264,000. All new RA patients are referred to the hospital for diagnosis and initiation of treatment. All patients older than 16 years with recent onset inflammatory arthritis who did not meet criteria or show clinical signs of other specific arthritides (crystal deposition disease, reactive arthritis, ankylosing spondylitis, psoriatic arthritis, etc.) were included in the 1997 RA inception cohort. These patients received rheumatology care at Jyväskylä Central Hospital for 2 years following diagnosis by a multidisciplinary team, including 5 rheumatologists, 7 nurse specialists, 4 trained physical therapists, an occupational therapist, a social worker, a nutritionist, and a podiatrist; patients were subsequently invited to participate in a study visit at 5 years.

**Treatment strategies.** Disease modifying antirheumatic drugs (DMARD) were started at time of diagnosis. Patients were treated according to the “sawtooth” strategy<sup>19–21</sup>. Target of therapy was clinical remission.

**Clinical and laboratory assessments.** Measures at baseline and at 2 and 5 years included 68 tender and 66 swollen joint counts<sup>22</sup>; laboratory tests including ESR, C-reactive protein, and rheumatoid factor (RF); self-reported pain and global health on 100 mm visual analog scale (VAS); functional capacity according to the Health Assessment Questionnaire, morning

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stiffness in minutes on self-report; and radiographs of the hands and feet. Wrists, metacarpophalangeal joints I–V, metatarsophalangeal joints I–V, and interphalangeal joints of the big toes were assessed according to Larsen score by an experienced rheumatologist (TS)<sup>23,24</sup>. Medications were recorded at each visit. The date of initiation and discontinuation of each DMARD was recorded.

**Definition of remission.** We used 3 separate sets of criteria to define remission at 5 years, as shown in the table below. The ACR remission criteria require: (1) no joint or tendon sheath swelling, (2) no joint tenderness, (3) normal ESR, (4) morning stiffness  $\leq$  15 minutes, and (5) no joint pain by history (we used VAS  $\leq$  10 mm on a scale of 1–100 mm)<sup>18</sup>. Fatigue was excluded, but the other 5 criteria were required. Clinical remission was defined as (1) no tender and (2) no swollen joints and (3) normal ESR. Radiographic remission was defined as (1) no worsening of erosions and (2) no new erosions from baseline to 5 years.

#### Remission criteria

ACR remission criteria in this study (criteria 1 to 5 must be fulfilled)

1. No joint swelling or soft tissue swelling of tendon sheets
2. No joint tenderness or pain on motion
3. Normal ESR of  $<$  30 in women and  $<$  20 in men
4. Morning stiffness  $\leq$  15 minutes
5. Absence of joint pain by history interpreted as pain VAS score  $\leq$  10 on a scale of 1–100
6. Absence of fatigue)

#### Clinical remission

1. No joint swelling
2. No joint tenderness or pain on motion
3. Normal ESR of  $<$  30 in women and  $<$  20 in men

#### Radiographic remission

1. No worsening of erosions
2. No new erosions from baseline to 5 years

**Statistical methods.** Data analyses were performed with SPSS 11.0 software (SPSS Inc., Chicago, IL, USA). Results are expressed as mean or median, standard deviation, or interquartile range (IQR). Confidence intervals (CI) were calculated using Clopper-Pearson's 95% confidence limits. The agreement of the remission criteria was tested using the Jaccard similarity index (Chamberlain's positive agreement), which calculates the proportion of positive observations in both variables over positive observations in either variable. The closer the Jaccard measure approaches 1, the better the agreement between variables. A nonparametric test for k related samples, Cochran's Q, was used to test the hypothesis that several related dichotomous variables (the 3 remission criteria) have the same mean.

## RESULTS

The study included 127 patients, with 111 patients participating in the 5-year control examination (9 patients had died, 4 patients declined to participate, 2 had moved, and in one case diagnosis had changed to ankylosing spondylitis). The mean age of the 127 patients at time of diagnosis was 56 years; 61% of the patients were women and the median duration of symptoms before diagnosis was 5 months (Table 1). More than half the patients were RF-positive, one-fourth had radiographic erosions in hands and/or feet, and 95 patients (75%) met ACR classification criteria<sup>25</sup> for RA at baseline. Cumulatively, 96 (87%) of the 111 patients who

Table 1. Patient characteristics at baseline in 127 patients with early RA.

|   |             |
|---|-------------|
| Age, yrs, mean (range)                                  | 56 (22, 85) |
| Female, n (%)   | 78 (61)     |
| Duration of symptoms before diagnosis, mo, median (IQR) | 5 (3, 11)   |
| RF positive, n (%)                                      | 68 (54)     |
| Met ACR 1987 criteria for RA, n (%)                     | 96 (75)     |
| Patients with erosions, n (%)                           | 32 (25)     |

completed the study met ACR criteria for RA over the 5 years; 9 new patients fulfilled the ACR criteria for RA during the 5-year followup period.

The number of patients in clinical remission at 2 and 5 years is shown in Figure 1. At 2 years, 48 [39% (95% CI 30% to 47%)] of the assessed patients were in remission. The corresponding figure at 5 years was 41 [37% (95% CI 28% to 47%)]. Only 23 patients [21% (95% CI 14% to 29%)] were in remission at 2 and 5 years (Figure 1).

At 5 years, 19 [17% (95% CI 11% to 25%)] of the 111 examined patients met ACR remission criteria, including 77 (69%) with no swollen joints, 48 (43%) with no tender joints, 83 (75%) with normal ESR, 53 (48%) with morning stiffness  $\leq$  15 minutes, and 26 (23%) patients with no pain (Table 2).

Forty-one patients [37% (95% CI 28% to 47%)] met the clinical remission criteria, and 61 patients [55% (95% CI 49% to 68%)] met radiographic remission criteria. Only 13 [12% (95% CI 6% to 19%)] patients met all 3 sets of remission criteria, and 74 [67% (95% CI 57% to 75%)] met at least one set of the criteria (Figure 2).

The similarity between the criteria was 0.46 (95% CI 0.31 to 0.62) for the ACR versus clinical remission, 0.19 (95% CI 0.10 to 0.29) for the ACR versus radiographic remission, and 0.38 (95% CI 0.27 to 0.49) for clinical versus radiographic remission criteria. The rate of remission was statistically significantly different using the 3 sets of remission criteria, also according to Cochran's Q ( $p <$  0.001).

Patients were actively treated with DMARD; the goal was to control inflammation, achieve remission, and prevent permanent joint damage. DMARD were started immediately at diagnosis. All but one of the 127 patients used DMARD, with the median (IQR) duration of DMARD therapy of 99% (91%, 100%) of the total followup time. Sulfasalazine was the first DMARD in 93 patients, while methotrexate (MTX), either alone or in different combinations, was initially instituted in 25 patients. During followup, 75 (59%) patients took MTX. The median (IQR) duration of MTX therapy (alone or combined with other DMARD) was 78% (52%, 96%) of followup time. A total of 69 (54%) patients used corticosteroids at some time during followup.

## DISCUSSION

The rate of remission was statistically significantly different

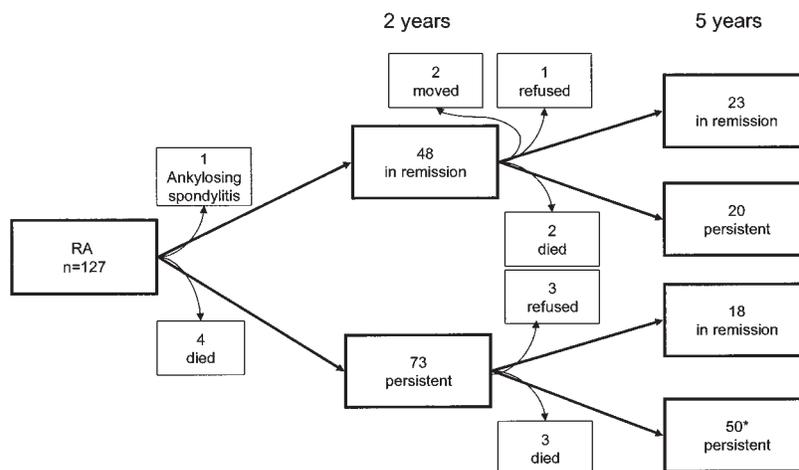


Figure 1. Clinical remission (no swollen joints, no tender joints, normal ESR) in a 1997 cohort of 127 patients with early RA. \*Includes one patient with no 2-year followup visit.

Table 2. ACR remission criteria in 111 patients with early RA at 5 years.

|  | N  | %  |
|--|----|----|
| ACR criteria                           |    |    |
| 1. No swollen joints                   | 77 | 69 |
| 2. No tender joints                    | 48 | 43 |
| 3. Normal ESR                          | 83 | 75 |
| 4. Morning stiffness $\leq 15$ minutes | 53 | 48 |
| 5. No pain (pain VAS $\leq 10$ mm)     | 26 | 23 |
| All 5 criteria                         | 19 | 17 |

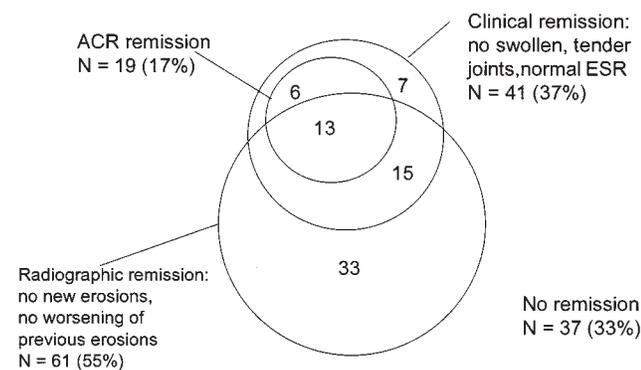


Figure 2. Remission in 111 patients with early RA 5 years after onset of disease.

( $p < 0.001$ ) using the 3 sets of remission criteria. The 5-year remission rate of 17% according to ACR criteria is within the wide range reported in the literature (reviewed below). As expected, the rate according to clinical remission criteria, which include 3 ACR remission criteria but not pain and morning stiffness (or fatigue), was considerably higher (35%) versus the ACR rate. A high percentage of 55% of

patients with no radiographic progression over 5 years was somewhat surprising, but similar to results of another cohort in our clinic<sup>26</sup>.

In previous studies remission rates in RA range from 0% to 42% (4–6, 8–18), depending on patients selected (population vs hospital based cohorts; early vs established disease), time followed, criteria applied, and therapy given. Prevoo, *et al*<sup>9</sup> followed 227 patients with longstanding RA for a median of 3.9 years, and found that the ACR remission was present in 9.5% of the 2832 visits in 227 patients in a hospital based patient cohort. In a study by Wolfe, *et al*<sup>6</sup>, 7.6% of patients were without symptoms at 7 years. Balsa, *et al*<sup>27</sup> reported that 7.9% of 788 patients with longstanding RA in 34 Spanish rheumatology centers were in ACR-defined remission (fatigue excluded).

In cohorts including patients with early RA, remission has been assessed according to the ACR criteria, as “clinical remission,” “being asymptomatic,” and “having no evidence of arthritis.” According to the ACR remission criteria, only 3% of patients in the study by Suarez-Almazor, *et al*<sup>13</sup> were in remission 6 to 7 years after diagnosis. A total of 85% had received DMARD, but only half of them within the first 2 years after onset. In the ERAS study<sup>10</sup>, 13% of patients with early RA were in remission at 5 years; in the Lund early RA cohort<sup>16</sup>, the remission rate was 18% at 10 years. Möttönen, *et al*<sup>28</sup> found that 32% of patients with early RA treated according to the “sawtooth” strategy were in remission at an average of 6.2 years after start of therapy. In the FIN-RACo trial, 42% of patients with early RA who were treated with a combination of DMARD including MTX were in remission at 2 years (fatigue omitted), while in patients treated with a single DMARD only 17% were in remission at 2 years<sup>8</sup>. The ACR remission criteria were also applied in a US early RA cohort of 232 patients, none of whom were in remission at an average of 1.8 years after the onset of disease<sup>18</sup>.

The rate of “clinical remission” was studied in a prospective, placebo controlled, double blind study including patients with early RA<sup>29</sup>. Only 2 of 40 patients (5%) who were treated with placebo reached clinical remission, while 9 of 38 patients (24%) who were initially treated with sulfasalazine were in remission at 48 weeks. In a study by Nissilä, *et al*<sup>4</sup>, 6.5% of patients with early RA were “asymptomatic” at 3 years. At that time only gold and hydroxychloroquine were commonly used to treat RA. By defining remission as “no evidence of arthritis on examination and no treatment with DMARD in preceding 3 months”, Harrison, *et al*<sup>5</sup> reported a remission rate of 19% at 2 years among patients with RA in a community-based inception cohort. In a study of Jäntti, *et al*<sup>7</sup>, radiographs of hands and feet were assessed according to Larsen score (scale 1–100). If the score did not worsen more than 1 point compared to radiographs taken 5–19 years earlier, a patient was considered to be in remission. Remission rate was 26% at 20 years.

Wolfe, *et al*<sup>30</sup> reported that sensitivity and specificity of the ACR remission criteria were good. Alarcon, *et al*<sup>31</sup> found specificity to be high, while sensitivity was low in some patient groups. Nevertheless, fatigue as a vaguely defined item is often excluded when the ACR remission criteria are used<sup>8,13,17</sup>. In some studies the criteria are considered to be met if all the other 5 items are fulfilled<sup>8,13,17</sup>, while in other studies only 4 of the remaining 5 items are required for remission<sup>15,16</sup>.

Similarly to many others, we excluded fatigue when we used the ACR remission criteria. Fatigue appears to be a nonspecific symptom. Wolfe, *et al* showed that clinically important levels of fatigue (VAS  $\geq 2$  on a scale 0–3) were present in more than 41% of patients with RA or osteoarthritis and in 76% of patients with fibromyalgia<sup>32</sup>; no significant associations were found between inflammatory process and fatigue. Morning stiffness and pain appear to be nonspecific symptoms also. Yazici, *et al*<sup>33</sup> observed that morning stiffness did not differ among patients with RA and osteoarthritis. Widespread musculoskeletal pain was reported by 24% of the 1002 community-dwelling elderly women in the US<sup>34</sup>. In the study by Mäntyselkä, *et al*<sup>35</sup> chronic pain was reported by 35.1% of the Finnish population age 15 to 74 years. The prevalence of pain increases with age. In our cohort, 22 patients with no swollen and tender joints and normal ESR did not meet ACR criteria because they did not meet criteria for pain and/or morning stiffness. It might be asked whether the status of these patients as not in remission was misclassified.

RA runs a fluctuating course. Less than 50% of our patients who were in clinical remission at 2 years were in remission also at 5 years. Molenaar, *et al*<sup>36</sup> followed RA patients in remission (by ACR remission criteria; fatigue was omitted and 4 of the 5 remaining items had to be fulfilled) for 2 years. Remission persisted in 52% of the patients after 2 years.

One could anticipate that radiographic remission would be the most rigorous of any remission criteria, since it has been shown that radiographic damage starts early and progression is most rapid during the first years of disease<sup>12,15,24,26,37-43</sup>. In a study by Lindqvist, *et al*<sup>38</sup> almost all (96%) RA patients had erosions at 10 years. In our study, a total of 42% of patients remained nonerosive throughout the 5-year followup period, and in the previous early RA cohorts in our clinic, 67% to 86% of patients had erosions within 5 years<sup>26</sup>.

As described above, the definition of remission among studies varies. The use of the ACR remission criteria is heterogeneous concerning fatigue and number of criteria required for remission, and it is questionable whether pain and morning stiffness criteria are related to RA. Clinical remission defined as no tender and no swollen joints and normal ESR<sup>44</sup> would well earn its place as the core set of remission criteria, as it has been shown that joint damage rarely occurs without clinically detectable inflammation<sup>45</sup>. As the ultimate goal of treatment is to prevent serious longterm consequences of RA such as joint damage, the concept of radiographic remission cannot be ignored as a potential criterion for remission. A set of remission criteria including no sign of inflammatory activity and no radiographic progression might be a basis for development of clinically relevant remission criteria for RA, possibly supplemented with a normal functional status suggested by Dr. Paulus in his recently published editorial<sup>46</sup>.

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