A good response to early DMARD treatment of patients with rheumatoid arthritis in the first year predicts remission during follow up

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OBJECTIVE: To describe the frequency and duration of remission in the Utrecht rheumatoid arthritis cohort of patients followed since diagnosis, and the clinical and treatment characteristics of patients with remission versus those without.

METHODS: In 1990 the Utrecht rheumatoid arthritis cohort study group started a clinical trial in which patients with recent onset of rheumatoid arthritis (<1 year) were randomised into four treatment groups: hydroxychloroquine (n = 169); intramuscular gold (n = 163); methotrexate (n = 166); and pyramidal (n = 64). After two years, rheumatologists were allowed to prescribe any disease modifying antirheumatic drug. Remission was defined as: duration of morning stiffness < 15 min, mean VAS pain < 10 mm, Thompson joint score < 10, and ESR < 30 mm/h during at least six months. Cox regression analysis was used to determine baseline clinical, demographic, and treatment predictors of remission.

RESULTS: Mean follow up duration was 62 months. Thirty six per cent achieved at least one period of remission. Median duration between diagnosis and the first remission period was 15 months for the intramuscular gold group, 18 months for the methotrexate and hydroxychloroquine groups, and 24 months for the pyramid group (NS). Predictors of remission were early response to initial treatment, less pain, rheumatoid factor negativity, and lower joint score at baseline.

CONCLUSIONS: After a mean follow up duration of 62 months, only 36% of the patients had fulfilled the remission criteria at least once. A good response to treatment during the first year seems to be independently associated with remission rather than initial treatment alone.

In this report we describe the frequency and duration of remission among patients participating in the Utrecht rheumatoid arthritis cohort. We investigated which baseline clinical, demographic, and treatment variables were possible predictors of remission and we describe the treatment before remission.

METHODS

From 1990 to 1998 all patients with recent onset of rheumatoid arthritis (less than one year) from six rheumatology outpatient clinics in the Utrecht region of the Netherlands were asked to participate in a randomised prospective clinical trial. All patients fulfilled the 1987 ACR criteria for rheumatoid arthritis.

TREATMENT

Patients were randomly assigned to the pyramid strategy group or to one of the three early DMARD strategy groups. All randomisation procedures were done by drawing sealed envelopes from blocks of 100 with equal numbers of patients for each of the four treatment groups per hospital. Patients in the pyramid group were treated with non-steroidal anti-inflammatory drugs (NSAIDs), and the administration of DMARDs started only if NSAIDs alone were clinically not effective enough after one year of treatment. After 1994 no further patients were allocated to the pyramid group because planned interim analysis showed that clinical efficacy after...
one year was significantly greater for the early DMARD strategy groups than for the pyramid group, making it unethical in our view to withhold treatment with DMARDs from the time of diagnosis in rheumatoid arthritis.

The three early DMARD strategy groups to which patients were randomly assigned were as follows:
- hydroxychloroquine group: treatment was started with hydroxychloroquine (400 mg/day), if necessary replaced by auranofin (6–9 mg/d);
- intramuscular gold group: intramuscular (im) gold (50750 mg/d);
- methotrexate group: oral methotrexate (7.5–15 mg/wk), if necessary replaced by sulphasalazine (2000–3000 mg/d).

Good response to the initially allocated DMARD was assessed one year after study start and was defined as more than 50% improvement from baseline in at least three of the following four disease indices: visual analogue scale (VAS) pain (mm), Thompson joint score (a weighted joint score following four disease indices: visual analogue scale (VAS) pain, morning stiffness (min), Thompson joint score, functional disability (health assessment questionnaire; HAQ), and erythrocyte sedimentation rate (ESR) (mm/h). Patients had to fulfil these criteria for at least six months—that is, three subsequent visits during the first two years, and then once every six months. The clinical variables were ESR, VAS general wellbeing, VAS pain, Thompson joint score, functional disability (health assessment questionnaire; HAQ), Dutch version⁶⁻⁷, and grip strength (based on the mean of three measurements in each hand using a vigrometer). If clinical data were missing, the mean of the previous and subsequent scores was used.

Rheumatoid factor status was determined at baseline and once every year thereafter, by either the latex fixation or the Rose-Waaler test (≥20 IU/ml). Radiographs of hands and feet were taken at baseline and once a year and scored according to the modified Sharp/van der Heijde method.⁸ If no radiological data were available for the last visit, the missing score was imputed by using the slope of radiological progression of the previous years. We believe that this method is valid, because a linear progression was found in a previous report that included this cohort of patients with rheumatoid arthritis.⁹

Definitions of remission, flare, and improvement
Remission was defined according to our adaptation of the remission definition of Scott et al., which was developed to evaluate the response to DMARDs more appropriately. In the present study, patients were considered to be in remission when the duration of morning stiffness was ≤15 minutes, VAS pain was ≤10 mm, Thompson joint score was ≤10, and ESR was ≤30 mm/h. Patients had to fulfil these criteria for at least six months—that is, three subsequent visits during the...
first two years or two subsequent visits after two years. The
design of our study committed us to include the Thompson
score as a substitute for the tender and swollen joint count.
Additional differences between our definition and that of
Scott are that we included <10 mm of pain instead of no
pain, and that the criteria had to be fulfilled for at least six
months. Patients who no longer fulfilled the remission
criteria during assessment were considered to have a flare at
that time.

Next to remission, we calculated the number of patients with
clinical improvement from baseline, using a modification
of the ACR20 criteria: a reduction of at least 20% from
baseline in the Thompson joint score and an improvement of
at least 20% from baseline in at least two of the following
four variables: patients’ assessment of pain (VAS), patients’
assessment of general wellbeing (VAS), patients’ assessment
of physical function (HAQ), and ESR.

Four years of follow up
To compare clinical and radiographic changes between
patients with at least one period of remission and those
without remission, and to identify baseline predictors of
remission, we evaluated the patients for whom four year
follow up data were available. For each treatment group
separately, we evaluated whether patients were responders
at one year by using the similar definition for a good re-
response as described above. After one year, the number of
responders with remission during the subsequent three
years was compared with number of non-responders with
remission.

Statistical analyses
Differences in median duration until the first period of
remission across the three treatment strategies were tested
for statistical significance using the Kruskall–Wallis test
(p<0.05).

After four years, mean (SD) and median changes from
baseline were calculated for all variables. Differences between
groups were tested by the unpaired two sided t test for
normal distribution of data or the Mann–Whitney U test for
non-normal distribution of data, where appropriate. Cox
logistic regression analysis was used to determine baseline
predictors of remission up to four years of follow up (stepwise
procedure).

Differences in the number of responders with remission
and the number of non-responders with remission at one
year were tested for statistical significance using the $\chi^2$ test.
All calculations were done using SPSS 9.0 software.

RESULTS
This study included 562 patients with rheumatoid arthritis
(70% women), whose mean (SD) age was 56 (14) years
at the start of the study. Baseline characteristics did not
differ between the four treatment strategy groups (table 1).
Mean follow up duration until the time of withdrawal or
until the last follow up visit available for the total study
population was 62 (24) months (range 12 to 96 months). Of
the 562 patients included in the study, 144 dropped out
during follow up. Causes of drop out were: death (42), moved
out of the area (11), other diseases which made adherence
to the cohort impossible (15), long lag time between this
study and the last outpatient visit (33), in remission or with
low disease activity (13), and otherwise, or reason unknown
(30).

Remission, flare, and improvement
In all, 205 patients (36%) achieved at least one period of
remission during follow up (57 patients had a second and
eight patients a third period of remission). Mean cumulative
duration of all remission periods was 25 (19) months (range
6 to 87), comprising 39 (25%) of total follow up time. Mean
duration from study start until the first period of remission
was 24 (19) months. Figure 1 shows the percentage of
patients in remission and the percentage of patients having a
flare at each assessment point. Of the 270 remission periods,
158 were followed by a flare; for 112 periods the data were
the last available data at time of evaluation of this study
(n = 84), or were the last data because patients dropped out
of the study or for various other reasons (n = 28).

Mean values of the following baseline characteristics were
significantly worse for patients without a period of remission
than for those with a period of remission: morning stiffness
(120 v 94), VAS general wellbeing (53 v 42), grip strength (28
v 36), Thompson joint score (157 v 128), VAS pain (52 v 36),
and HAQ (1.4 v 1.1). The percentage of patients with absent
rheumatoid factor at baseline was significantly higher among
patients with remission than in those without (45% v 29%).
Age (56 v 57), ESR (43 v 39), and radiographic damage (3.9 v
4.8) did not differ significantly between the two groups. In
addition, the area under the curve standardised to time for all
clinical variables was significantly worse for the non-
remission group than for the remission group (mean scores:
ESR, 27 v 16; morning stiffness, 65 v 18; VAS general
wellbeing, 40 v 18; grip strength, 34 v 56; Thompson joint
score, 70 v 23; VAS pain, 32 v 9; functional disability, 1.30 v
0.62).

The percentage of patients in remission during follow up
was not significantly different (p = 0.28) between the four
therapy strategy groups: 42% in the im gold group, 36% in
the methotrexate group, 31% in the hydroxychloroquine
and 38% in the pyramid group. Although not
statistically significant, the median time until the first
remission period tended to differ between the four assigned
treatment strategy groups (p = 0.078). Mean (SD) time until
the first remission for the im gold group was 21 (17) months
(median 15), v 24 (19) months for the methotrexate group
(median 18), 24 (19) months for the hydroxychloroquine
group (median 18), and 33 (23) months for the pyramid
group (median 24).

In all, 16 patients (8%) did not receive any DMARD during
the six months before their first period of remission. The
numbers (%) of patients receiving each specific DMARD
before remission were: im gold, 55 (27%); methotrexate, 70
(34%); hydroxychloroquine, 42 (21%); D-penicillamine, 8
(4%); sulphasalazine, 8 (4%); azathioprine, 1 (<1%); and com-
binations of DMARDs, 7 (3%). In the overall study population,
99% of the patients used NSAIDs, 22% used prednisone or dexamethasone, and 57% received an
intra-articular injection during follow up. In the remission
group, eight patients (4%) received prednisone or dexamethasone in the period before the visit of the
remission period and the previous visit, and 19 patients (9%)
received at least one intra-articular injection at the visit prior
to the remission period.

Clinical improvement from baseline to one year was
achieved by 64% patients in the im gold group, 71% in the
methotrexate group, 59% in the hydroxychloroquine
and 47% in the pyramid group (p = 0.005). Thereafter, a
significant difference in the number of patients with clinical
improvement at predefined assessment points from baseline
(p<0.05) was observed between the initial four treat-
ment groups at 15 months (73%, 75%, 59%, and 54% of
the patients, respectively), 18 months (74%, 71%, 57%,
and 55%), 21 months (72%, 75%, 66%, and 57%), 48 months
(76%, 77%, 74%, and 56%), and 60 months (75%, 72%, 68%,
and 64%). At other time points no significant differences
were found in the number of patients with improvement
from baseline.
Four years of follow up

Data on 425 patients with rheumatoid arthritis were available at four years (table 2). At least one period of remission was achieved in 142 patients (33%). Patients who were in remission during the first four years of their disease had a more favourable disease course with respect to all measured variables than those who were not, irrespective whether these variables were part of the remission definition or not (table 3).

Considering each treatment strategy separately, treatment responders (≥50% improvement on three of four variables) at the one year follow up were compared with non-responders. Baseline values did not differ between the responder group and the non-responder group, except for age and ESR in the methotrexate group. In the group of patients who received imogol at baseline, 55% of the responders (n = 67) and 16% of the non-responders (n = 57) were in remission at some assessment point in the subsequent three years (p = 0.001). In the methotrexate group these percentages were 51% of 63 patients and 13% of 60 patients (p = 0.001), respectively; in the hydroxychloroquine group, they were 52% of 48 patients and 18% of 78 patients (p = 0.0001), and in the pyramid group they were 67% of 15 and 19% of 37 patients (p = 0.001). This indicates that despite similar baseline characteristics and

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients without a period of remission (n = 283)</th>
<th>Patients with ≥1 period of remission (n = 142)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), median</td>
<td>56 (14)</td>
<td>60 (15)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>55 (14)</td>
<td>58 (15)</td>
<td>NS</td>
</tr>
<tr>
<td>Female sex</td>
<td>71%</td>
<td>65%</td>
<td>NS</td>
</tr>
<tr>
<td>ESR (mm/h), median</td>
<td>37</td>
<td>34 (34)</td>
<td>NS</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>42 (27)</td>
<td>42 (29)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Morning stiffness (min), median</td>
<td>90</td>
<td>60</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>113 (130)</td>
<td>94 (122)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Pain (mm), median</td>
<td>50</td>
<td>30</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>50 (26)</td>
<td>35 (21)</td>
<td>NS</td>
</tr>
<tr>
<td>Joint score (Thompson), median</td>
<td>127</td>
<td>113</td>
<td>NS</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>153 (110)</td>
<td>132 (95)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Rheumatoid factor positive</td>
<td>74%</td>
<td>54%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>VAS, general wellbeing (mm), median</td>
<td>52</td>
<td>47</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>53 (24)</td>
<td>43 (28)</td>
<td>NS</td>
</tr>
<tr>
<td>Grip strength (kPa), median</td>
<td>27</td>
<td>32</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>30 (20)</td>
<td>36 (21)</td>
<td>NS</td>
</tr>
<tr>
<td>Functional disability (HAQ), median</td>
<td>1.4</td>
<td>1.0</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>1.4 (0.7)</td>
<td>1.2 (0.8)</td>
<td>NS</td>
</tr>
<tr>
<td>Radiographic damage (Sharp/van der Heijde score), median</td>
<td>2.0</td>
<td>2.5</td>
<td>NS</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>5 (8)</td>
<td>5 (8)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Baseline values did not differ between the responder group and the non-responder group, except for age and ESR in the methotrexate group. In the group of patients who received imogol at baseline, 55% of the responders (n = 67) and 16% of the non-responders (n = 57) were in remission at some assessment point in the subsequent three years (p = 0.001). In the methotrexate group these percentages were 51% of 63 patients and 13% of 60 patients (p = 0.001), respectively; in the hydroxychloroquine group, they were 52% of 48 patients and 18% of 78 patients (p = 0.0001), and in the pyramid group they were 67% of 15 and 19% of 37 patients (p = 0.001). This indicates that despite similar baseline characteristics and

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<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variables included in definition of remission ESR (mm/h), median</td>
<td>−16</td>
<td>−21</td>
<td>0.011</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>−19 (27)</td>
<td>−28 (28)</td>
<td>0.030</td>
</tr>
<tr>
<td>Morning stiffness (min), median</td>
<td>−30</td>
<td>−60</td>
<td>NS</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>−53 (172)</td>
<td>−78 (133)</td>
<td>NS</td>
</tr>
<tr>
<td>Pain (mm), median</td>
<td>−18</td>
<td>−26</td>
<td>0.001*</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>−20 (32)</td>
<td>−30 (29)</td>
<td>0.012</td>
</tr>
<tr>
<td>Joint score (Thompson), median</td>
<td>−85</td>
<td>−106</td>
<td>NS</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>−99 (119)</td>
<td>−125 (98)</td>
<td>NS</td>
</tr>
<tr>
<td>Variables not included in definition of remission VAS general wellbeing (mm), median</td>
<td>−16</td>
<td>−25</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>−15 (30)</td>
<td>−28 (29)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Grip strength (kPa), median</td>
<td>8</td>
<td>24</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>8 (22)</td>
<td>21 (21)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Functional disability (HAQ), median</td>
<td>0</td>
<td>−0.6</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>−0.1 (0.7)</td>
<td>−0.6 (0.7)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Radiographic damage (Sharp/van der Heijde score), median</td>
<td>−22</td>
<td>−11</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>−34 (34)</td>
<td>−20 (25)</td>
<td>NS</td>
</tr>
</tbody>
</table>

†Significant different between the group of patients with remission and group of patients without remission using unpaired two sided t test for normally distributed data [*] and Mann–Whitney U test for non-normally distributed data. Ranges for variables are as follows: ESR, 1 to 140; morning stiffness, 0 to 720; pain, 0 to 100 = worst score; joint score, 0 to 534; general wellbeing, 0 to 100 = worst score; grip strength, 0–120 = best score; functional disability, 0 to 3 = worst score; radiographic damage, 0 to 448. ESR, erythrocyte sedimentation rate; HAQ, health assessment questionnaire; VAS, visual analogue scale.
similar treatment, patients are more likely to achieve remission when they were defined as responders at one year, as one would expect.

For determining predictors of remission, complete baseline data were available on 397 patients. Baseline predictors of remission were a good response to treatment, less pain, absence of rheumatoid factor, and lower joint score (table 4).

**DISCUSSION**

In this cohort of patients with rheumatoid arthritis followed since diagnosis, we show that 36% of 562 patients achieved at least one period of remission during follow up and that patients were in remission for 39% of their follow up time. The latter percentage is slightly higher than found in the study by Eberhardt and Fex, where 62% of the patients were in remission for 39% of their follow up time. Since diagnosis, we show that 36% of 562 patients achieved at least one period of remission during follow up study comparing combination therapy with methotrexate (15 mg/week, which has greater efficacy). Furthermore, conventional DMARDs probably remain the rheumatologists’ first choice because of the lack of availability of biological agents in certain countries and their high cost.

In this study, remission was more likely to occur in patients with a good response to the initial treatment strategy, in those who were initially rheumatoid factor negative, and in those with less pain and a lower joint count at baseline. In several other studies the absence of rheumatoid factor was also found to be associated with an increased probability of remission, while rheumatoid factor positivity is associated with radiological damage. Not many studies have estimated the influence of treatment as an independent predictor of remission. In a two year follow up study comparing combination therapy with single drug therapy, the combination treatment regimen was found to be the only variable predicting remission after two years.

Although time until the first remission period tended to differ between the four assigned treatment groups at baseline, the kind of DMARD at baseline did not predict remission. We did find that the frequency of remission after one year was significantly higher among responders than among the non-responders.

**Conclusions**

After a mean follow up duration of 62 months, only 36% of the patients had fulfilled the remission criteria at least once. Good response to treatment, less pain, a negative rheumatoid factor test, and a lower joint count at baseline were predictors of remission, but not the allocated first drug. It thus seems that a good response to treatment during the first year is linked to the likelihood of going into remission rather than to the type of initial treatment given. This suggests that treatment should be tailored to the individual patient and that we should aim for a rapid response using aggressive treatment strategies such as higher doses of methotrexate.

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**Table 4** Baseline predictors of remission during four years of follow up using Cox regression analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>B</th>
<th>SE</th>
<th>p Value</th>
<th>Exp (β)</th>
<th>95% CI, Exp (β)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good response</td>
<td>1.56</td>
<td>0.20</td>
<td>0.000</td>
<td>4.75</td>
<td>3.20 to 7.03</td>
</tr>
<tr>
<td>Pain</td>
<td>−0.02</td>
<td>0.04</td>
<td>0.000</td>
<td>0.98</td>
<td>0.97 to 0.99</td>
</tr>
<tr>
<td>Rheumatoid factor negative</td>
<td>0.49</td>
<td>0.18</td>
<td>0.061</td>
<td>1.63</td>
<td>1.15 to 2.32</td>
</tr>
<tr>
<td>Joint score</td>
<td>−0.002</td>
<td>0.00</td>
<td>0.048</td>
<td>1.00</td>
<td>0.996 to 1.00</td>
</tr>
</tbody>
</table>

Complete baseline data on 397 patients were available for this analysis.

CI, confidence interval.

Good response, more than 50% improvement from baseline on at least three of four disease parameters (mean VAS pain, joint score, morning stiffness, or ESR).

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We would like to thank all the other participating rheumatologists of the Utrecht Rheumatoid Arthritis Cohort study group; C van Booma-Frankfort (Diakonessenhuis, Utrecht), E J ter Borg (Antonius Hospital, Nieuwegein), A H M Heukens (Meander Medical Centre, Amersfoort), D H M van der Heijden (Hilversum Hospital, Hilversum), A A Kruize (UHMC Utrecht, Utrecht), M J van der Veen (St Jansdal, Harderwijk), and C M Verhoef (Flevo hospital, Almere), Netherlands.

REFERENCES


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