Do short and sustained periods of ACR/EULAR remission predict good functional and radiographic outcome in early rheumatoid arthritis patients with low overall damage progression?

Nicole Konijn, Lilian van Tuyl, Maarten Boers, Debby den Uyl, Marieke ter Wee, Pit Kerstens, Alexandre Voskuyl, Dirkjan van Schaardenburg, Michael Nurmohamed and Willem Lems

Arthritis Care Res (Hoboken) 2017 Jul;69(7):989-996
**Objective:** To investigate whether remission at single and consecutive visits predicts good outcome in early rheumatoid arthritis (RA).

**Methods:** The presence of remission according to ACR/EULAR and other criteria (Boolean clinical, CDAI, DAS, DAS28, RAPID3) was assessed in early RA patients during the first year of the COBRA-light trial. Likelihood ratios were used to assess whether meeting the remission criteria at single visits (13, 26, 39 or 52 weeks) and consecutive visits (13+26, 26+39 or 39+52 weeks) predicted good outcome in the second year (52-104 weeks). Good outcome was defined for function (HAQ consistently ≤0.5 and no deterioration), radiographic damage progression (no deterioration in Sharp-Van der Heijde Scores) and both (‘overall good outcome’).

**Results:** Of the original 164 trial patients, 144 had evaluable data. In the second year, good functional outcome was observed in 35%, good radiographic outcome in 79%, and both in 28% of the patients. Almost all criteria predicted good functional and good overall outcome, at both single and consecutive visits; only single DAS remission did not significantly predict good overall outcome (p=0.07). Sustained remission periods resulted in higher likelihood ratios than remission at single visits. None of the criteria predicted good radiographic outcome.

**Conclusion:** Early RA patients who reached remission according to ACR/EULAR and other criteria during short or sustained periods were likely to retain good physical function in the subsequent months. Sustained remission periods were a stronger predictor than remission at single visits. However, in the setting of low overall damage progression, (sustained) remission was not predictive of good radiographic outcome.
Validation of remission criteria in early RA

Introduction

Patients with rheumatoid arthritis (RA) who achieve a state of remission show less deterioration in functional and radiographic outcomes than patients who do not reach a state of remission.\(^1\) Over the past years, remission rates have increased, due to advances in therapy including biologic agents and new combination therapy strategies such as BEST, COBRA, and COBRA-light.\(^1\) Remission may now be a feasible target for RA patients, which is reflected in the latest recommendations for RA management.\(^8\)\(^-\)\(^11\)

Remission is not only a major therapeutic target in clinical practice, but also a primary or secondary end point in clinical trials.\(^2\)\(^,\)\(^3\)\(^,\)\(^12\)\(^-\)\(^16\) The definition of remission often differs between studies, resulting in the measurement of different aspects of disease state.\(^2\)\(^,\)\(^3\) In 2011, a committee of the American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) was constituted to form a new, uniform, easy-to-use definition of remission. The committee validated candidate remission definitions to their potential to predict good functional and radiographic outcome in future, which resulted in two new definitions of remission: a Boolean-based definition and an index-based alternative, both able to predict RA prognosis.\(^2\) Nevertheless, other definitions are still being used.

A feature of the ACR/EULAR remission criteria is that it, intentionally, has no minimum duration requirement, as the committee felt that such a requirement could only be based on prospective validation once the criteria were in place, including information on the frequency of assessment. However, RA is a chronic, progressive and destructive disease, with disease activity over time as best predictor of progression and destruction;\(^17\)\(^-\)\(^19\) it is a given that duration of remission matters. Patients have also identified duration as an important aspect of the concept of remission.\(^20\)

Thus, the ACR/EULAR criteria were only validated for remission at one point in time, although sustained remission could be an even stronger predictor of RA prognosis. Furthermore, the patients in the validation study mainly had established RA, whereas results might be different for early RA patients. Therefore, our study aimed to investigate, in the context of the COBRA-light trial, whether remission (according to ACR/EULAR and other criteria) at single and consecutive visits could predict good outcome in early RA.

Patients and methods

Study design and study population

This study was part of the larger multicenter COBRA-light trial, which assessed the non-inferiority of ‘COBRA-light’ versus COBRA therapy on clinical and radiologic outcomes in 164 early RA patients (ISRCTN Clinical Trial Registration Number: 55552928).\(^4\)\(^,\)\(^21\) In brief, COBRA-light therapy (prednisolone 30 mg/day, tapered to 7.5 mg/day in 8 weeks and MTX escalated to 25/mg week in 8 weeks) was compared with COBRA therapy (prednisolone...
60 mg/day, tapered to 7.5 mg/day in 6 weeks, MTX 7.5 mg/week and SSZ 2 g/day), with Disease Activity Score in 44 joints (DAS) <1.6 as treatment goal.

Patients visited their study center at baseline and 13, 26, 39, 52, 78 and 104 weeks after start of treatment. In the period of 26 to 52 weeks; treatment intensification of MTX and addition of etanercept was protocolled. After 52 weeks, treatment was continued without protocol, and therapy was adjusted by the treating physician according to clinical judgment. Intra-articular and intramuscular glucocorticoid injections were allowed, and for possible influence on disease activity assessments was corrected, as reported earlier.21

Eligibility criteria, randomisation process and study design have been reported previously.4 Medical ethics committees at each participating centre approved the protocol; patients gave written informed consent, and the study was conducted in accordance with the Declaration of Helsinki/Good Clinical Practice.

Functional and radiographic outcome

The Dutch consensus version of the Health Assessment Questionnaire (HAQ)22 assessed physical function at each visit, except at 39 weeks. Radiographs of both hand and feet were obtained at baseline and at 26, 52 and 104 weeks after start of treatment, and scored by two independent trained assessors according to the Sharp-Van der Heijde Score (SHS) method.23 Details about the SHS scoring method were reported earlier.4,21

Remission criteria

Remission was defined according to the criteria below and assessed at every visit after baseline. ACR/EULAR criteria are summarized as follows: 1) Boolean: tender joint count (based on 53 joints) ≤1, swollen joint count (based on 44 joints) ≤1, C-reactive protein (CRP) level ≤1 mg/dl, and patient global assessment (0–10 scale) ≤1;2 and 2) the Simplified Disease Activity Index (SDAI): sum of tender joint count (based on 28 joints), swollen joint count (based on 28 joints), patient and physician global assessment (0–10 scale), and CRP level ≤3.3 mg/dl.2,24 Other criteria are summarized as follows: 1) Boolean clinical: tender joint count (based on 53 joints) ≤1, swollen joint count (based on 44 joints) 1, and patient global assessment (0–10 scale) ≤1;2 2) Clinical Disease Activity Index (CDAI): sum of tender joint count (based on 28 joints), swollen joint count (based on 28 joints), and patient and physician global assessment (0–10 scale) ≤2.8;2,25 3) DAS≤1.6;26 4) DAS28≤2.6;27 and 5) Routine Assessment of Patient Index Data 3 (RAPID-3): sum of HAQ, patient assessment of pain, and patient global assessment (0–30 scale) ≤3.0.28-30

Sustained remission was defined as the fulfilment of remission criteria on two consecutive visits (i.e. 13+26, 26+39 or 39+52 weeks). RAPID3 remission could not be calculated at week 39, as no HAQ was assessed at this visit. Therefore, sustained RAPID3 remission was calculated at 13+26 weeks and 26+52 weeks.
Validation of remission criteria

Following the methodology of the ACR/EULAR committee, the predictive value of each remission definition for the second year was assessed. We hypothesized that patients who met a particular definition of remission at least once at 13, 26, 39 and/or 52 weeks would be more likely to have a good outcome in the second year of the trial than patients who were never in remission. Applying the same definitions used in the original ACR/EULAR validation study, good physical function (ΔHAQ ≤ 0 and HAQ consistently ≤ 0.5) and good radiographic outcome (ΔSHS ≤ 0) were both tested as separate outcomes and combined together (‘good overall outcome’).

Likewise, we hypothesized that patients who experienced ‘sustained remission’ at two consecutive visits at least once at 13+26, 26+39 or 39+52 weeks would be more likely to have a good outcome in the second year of the trial, than patients who were never in sustained remission.

Radiographic outcome was scored by two independent assessors, and the mean score of both assessors was reported. In cases where one assessor scored 1 SHS unit of progression and the other assessor scored 0, the mean would be 0.5. Such cases could also be considered as ‘stable’. Therefore, a sensitivity analysis was performed where absence of radiologic progression was defined as ≤ 0.5 SHS units.

Missing data

Dropouts during the 104 weeks treatment period after baseline (n=13) and patients with missing data on elements of the DAS, HAQ, SHS, ESR, CRP and VAS assessments at ≥ 2 visits at week 13, 26, 39, 52, 78 and 104 (n=7) were excluded from the analyses.

Missing data on elements of the DAS, HAQ, SHS, ESR, CRP and VAS assessments at one of the visits were imputed to a predefined protocol: a missing value at an in-between visit was replaced by the parameter’s mean score of the visit before and after the missing visit. A missing value at week 104 was predicted via the trend of simple linear regression over all earlier visits, by using the data of the single patient only (n=1).

Missing data was also imputed via the Last Value Carried Forward (LVCF) method: a missing value was replaced by the value of the last available visit. The LVCF method is considered conservative, as improvement was expected over time.

In total, 1% (96/8640 data points) of the above reported variables were imputed. Sensitivity analyses were performed to evaluate the influence of both imputation methods.

Statistical analyses

Data are presented as mean (standard deviation), or median [25th percentile, 75th percentile] in case of skewed data, unless otherwise specified.

Generalised Estimating Equations (GEE) was used to assess changes in disease activity, physical functioning and radiologic outcome over time, correcting for repeated measures. DAS was analysed with linear GEE analysis. Skewed HAQ data was log transformed before
linear GEE analysis. SHS data was extremely skewed and Poisson regression was not possible because of overdispersion. SHS data was therefore analysed with two different methods: 1) as counts outcome with the negative binomial (log link) distribution, and 2) as dichotomous outcome (radiologic damage: yes/no) with the binomial distribution. The exchangeable correlation matrix was used in all analyses. β or odds ratio’s (OR), and 95% confidence intervals (CI) are reported.

Following the methodology of the ACR/EULAR committee, positive likelihood ratios (LR) were used to compare the proportion of patients having the good outcome whose RA was in remission at least once, with the proportion of patients having the good outcome whose RA was never in remission, both at single visits (versus never remission at 13, 26, 39 or 52 weeks) and according to the three defined periods of sustained remission (versus never sustained remission at 13+26, 26+39 or 39+52 weeks). The p-values from logistic regression chi-square tests were used. While we have made association models, we do use the term ‘predict’ throughout the manuscript, as our main outcomes lie in the future.

All statistical analyses were performed with IBM SPSS Statistics, release 22.0 (SPSS Inc, Chicago, Illinois, United States). P-values<0.05 were considered significant.

**Results**

**Main clinical outcomes**

In this study, 144 early RA patients of the COBRA-light trial (88% of original trial population; 68% women, mean age 52 year) were included for analyses (Table 1). During the two year follow-up period of the trial, mean DAS decreased significantly from 4.0 at baseline, to 1.8 after 52 weeks, and 1.7 after 104 weeks (GEE over time: β=-0.17, CI=-0.19;0.15, p<0.001) (Figure 1). Median HAQ decreased significantly from 1.3 at baseline, to 0.4 after 52 weeks, and 0.5 after 104 weeks (GEE over time: β=-0.02, CI=-0.03;0.02, p<0.001). Median SHS increased significantly from 0 at baseline, to 0.5 after 52 weeks, and 1.0 after 104 weeks (GEE over time: 1) counts outcome: OR=1.05, CI=1.03;1.06, p<0.001; 2) dichotomous outcome: OR=1.08, CI=1.05;1.12, p<0.001).
### TABLE 1. Baseline patient characteristics and remission criteria over time (n=144)

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Week 13</th>
<th>Week 26</th>
<th>Week 39</th>
<th>Week 52</th>
<th>Week 78</th>
<th>Week 104</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female, n (%)</td>
<td>98 (68)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Age in years</td>
<td>52 (13)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Disease duration in weeks</td>
<td>16 [9;30]</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Sharp - Van der Heijde Score</td>
<td>0 [0;2.0]</td>
<td>0.3 [0;2.0]</td>
<td>-</td>
<td>0.5 [0;2.9]</td>
<td>-</td>
<td>1.0 [0;3.0]</td>
<td>-</td>
</tr>
<tr>
<td>HAQ</td>
<td>1.3 [0.9;1.8]</td>
<td>0.5 [0;1.0]</td>
<td>0.4 [0;1.0]</td>
<td>-</td>
<td>0.4 [0.9]</td>
<td>0.5 [0;1.0]</td>
<td>0.5 [0;1.1]</td>
</tr>
<tr>
<td>DAS</td>
<td>4.0 [0.8]</td>
<td>1.9 [1.1]</td>
<td>1.7 [1.1]</td>
<td>1.7 [1.0]</td>
<td>1.8 [1.0]</td>
<td>1.7 [1.1]</td>
<td>1.7 [1.1]</td>
</tr>
<tr>
<td>Tender joint count in 53 joints</td>
<td>14 [9;19]</td>
<td>3 [0;9]</td>
<td>2 [0;6]</td>
<td>2 [0;6]</td>
<td>3 [0;8]</td>
<td>2 [0;7]</td>
<td>2 [0;8]</td>
</tr>
<tr>
<td>Swollen joint count in 44 joints</td>
<td>13 [9;17]</td>
<td>2 [0;6]</td>
<td>2 [0;4]</td>
<td>1 [0;4]</td>
<td>1 [0;4]</td>
<td>1 [0;4]</td>
<td>1 [0;4]</td>
</tr>
<tr>
<td>DAS28</td>
<td>5.4 [1.1]</td>
<td>2.7 [1.3]</td>
<td>2.4 [1.3]</td>
<td>2.4 [1.3]</td>
<td>2.6 [1.3]</td>
<td>2.5 [1.3]</td>
<td>2.5 [1.3]</td>
</tr>
<tr>
<td>Tender joint count in 28 joints</td>
<td>8 [5;12]</td>
<td>1 [0;4]</td>
<td>1 [0;3]</td>
<td>1 [0;3]</td>
<td>1 [0;4]</td>
<td>1 [0;3]</td>
<td>1 [0;3]</td>
</tr>
<tr>
<td>Swollen joint count in 28 joints</td>
<td>8 [6;12]</td>
<td>1 [0;4]</td>
<td>1 [0;3]</td>
<td>1 [0;3]</td>
<td>1 [0;2]</td>
<td>1 [0;2]</td>
<td>0 [0;2]</td>
</tr>
<tr>
<td>Patient global assessment</td>
<td>6.1 [4.3;7.7]</td>
<td>2.2 [0.5;4.7]</td>
<td>2.0 [0.5;4.8]</td>
<td>2.6 [0.6;5.0]</td>
<td>2.2 [0.7;4.9]</td>
<td>2.2 [0.6;5.0]</td>
<td>2.2 [0.6;5.1]</td>
</tr>
<tr>
<td>Patient assessment of disease activity</td>
<td>6.6 [5.0;8.0]</td>
<td>1.6 [0.3;3.9]</td>
<td>1.6 [0.3;4.5]</td>
<td>1.9 [0.4;5.1]</td>
<td>1.5 [0.4;4.8]</td>
<td>1.7 [0.4;4.2]</td>
<td>1.5 [0.6;5.2]</td>
</tr>
<tr>
<td>Physician assessment of pain</td>
<td>6.1 [4.0;7.6]</td>
<td>1.7 [0.3;3.1]</td>
<td>1.6 [2.2;4.5]</td>
<td>2.1 [0.4;4.7]</td>
<td>1.8 [0.4;4.7]</td>
<td>1.8 [0.4;4.8]</td>
<td>1.9 [0.6;5.1]</td>
</tr>
<tr>
<td>Physician assessment of disease activity</td>
<td>4.8 [4.0;6.0]</td>
<td>1.6 [0.8;2.5]</td>
<td>1.1 [0.5;2.5]</td>
<td>1.3 [0.5;2.5]</td>
<td>1.5 [0.5;2.6]</td>
<td>1.3 [0.4;2.7]</td>
<td>1.5 [0.5;2.3]</td>
</tr>
</tbody>
</table>

Data are presented as mean (standard deviation) for normally distributed variables and as median [25th percentile, 75th percentile] for non-parametric variables, unless otherwise specified; Patient and physician assessments by visual analogue scale (VAS) in cm; CRP = C-reactive protein; DAS = Disease Activity Score of 44 joints, DAS28 = Disease Activity Score of 28 joints; ESR = Erythrocyte Sedimentation Rate, and HAQ = Health Assessment Questionnaire.

### FIGURE 1. Main clinical outcomes in early RA patients during the two year follow-up period of the COBRA-light trial (n=144)

*Significant change over time in GEE analyses (p<0.05); DAS = Disease Activity Score of 44 joints, HAQ = Health Assessment Questionnaire, and SHS = Sharp - Van der Heijde Score*
Chapter 3

Remission

Highest mean remission rates over the two-year follow-up period of the COBRA-light trial were observed for DAS28 (55%), followed by DAS (44%), CDAI and SDAI (28%), RAPID3 (21%), and Boolean clinical and Boolean criteria (19%) (Figure 2).

Highest sustained remission rates at 13+26, 26+39, and 39+52 weeks were observed for DAS28 (40-43%), followed by DAS (32-38%), SDAI (15-17%), CDAI (14-17%), Boolean clinical (8-9%) and Boolean (7-8%) criteria. Rates for RAPID3 remission were 11% at 13+26 weeks and 13% at 26+52 weeks (Figure 3).

Predictive value of remission

Between 52 and 104 weeks of follow-up, good functional outcome was observed in 51 patients (35%), good radiographic outcome in 114 patients (79%), and both in 40 patients (28%). In the group of patients with radiologic progression (21%), median increase in SHS was 1.3 [0.5;2.0], with a minimum increase of 0.5 and maximum of 5.0 SHS units. Radiologic progression >0.5 SHS units was observed in 13% of the patients.

Patients who were in remission at least once during the first trial year were more likely to experience good functional and good overall outcome between 52 and 104 weeks follow-up, than patients who were never in remission (Table 2). This applied to all remission criteria, except for the prediction of good overall outcome by DAS (p=0.07).
Likewise, patients who were in sustained remission at least once during the first trial year were more likely to experience good functional and good overall outcome between 52 and 104 weeks follow-up, than patients who were never in sustained remission (Table 3). This applied to all remission criteria.

At both single and consecutive visits, the prediction of good functional outcome resulted in higher LRs than the prediction of good overall outcome. Boolean, Boolean clinical, and RAPID3 criteria demonstrated the highest LRs for good functional outcome, followed by CDAI and SDAI, and DAS and DAS28. A similar trend was demonstrated for good overall outcome.

In contrast to above, none of the remission criteria were predictive of good radiographic outcome between 52 and 104 weeks follow-up in the context of low overall radiologic damage progression, although changing the cut-off for progression to 0.5 increased the LRs, with that of 2 associations becoming significant (data not shown).

Non-imputed and LVCF-imputed data demonstrated comparable LRs for both single and sustained periods of remission (data not shown).
TABLE 2. Predictive value of remission at single visits during the first treatment year for good RA prognosis during the second treatment year in early RA patients of the COBRA-light trial (n=144)

<table>
<thead>
<tr>
<th>Remission criteria</th>
<th>Good functional outcome $^\dagger$</th>
<th>Good radiographic outcome $^\ddagger$</th>
<th>Good overall outcome $^¥$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LR+  $^£$  95% CI  p-value $^¥$</td>
<td>LR+  95% CI  p-value</td>
<td>LR+  95% CI  p-value</td>
</tr>
<tr>
<td>Boolean</td>
<td>3.6  2.3;5.7  &lt;0.001*</td>
<td>1.3  0.7;2.4  0.34</td>
<td>2.8  1.9;4.1  &lt;0.001*</td>
</tr>
<tr>
<td>Boolean clinical</td>
<td>3.3  2.1;5.0  &lt;0.001*</td>
<td>1.2  0.7;2.1  0.48</td>
<td>2.6  1.8;3.8  &lt;0.001*</td>
</tr>
<tr>
<td>CDAI</td>
<td>2.3  1.7;3.1  &lt;0.001*</td>
<td>1.2  0.8;1.9  0.41</td>
<td>2.0  1.5;2.6  &lt;0.001*</td>
</tr>
<tr>
<td>SDAI</td>
<td>2.3  1.7;3.1  &lt;0.001*</td>
<td>1.3  0.9;2.1  0.22</td>
<td>2.1  1.6;2.8  &lt;0.001*</td>
</tr>
<tr>
<td>DAS</td>
<td>1.4  1.1;1.6  &lt;0.001*</td>
<td>1.0  0.8;1.3  0.84</td>
<td>1.2  1.0;1.5  0.07</td>
</tr>
<tr>
<td>DAS28</td>
<td>1.4  1.2;1.6  &lt;0.001*</td>
<td>1.1  0.9;1.4  0.32</td>
<td>1.3  1.2;1.5  0.001*</td>
</tr>
<tr>
<td>RAPID3 $^§$</td>
<td>3.5  2.3;5.6  &lt;0.001*</td>
<td>0.9  0.5;1.5  0.68</td>
<td>2.7  1.8;4.0  &lt;0.001*</td>
</tr>
</tbody>
</table>

$^\dagger$ Good functional outcome = $\Delta$HAQ≤0 and HAQ consistently ≤0.5 between 52 and 104 weeks; $^\ddagger$ Good radiographic outcome = $\Delta$SHS≤0 between 52 and 104 weeks; $^¥$ Good overall outcome = good functional and good radiographic outcome between 52 and 104 weeks.

Positive likelihood ratios were calculated to compare the proportion of patients having the good outcome whose RA was at least once in remission to the proportion of patients having the good outcome whose RA was never in remission at 13, 26, 39 or 52 weeks; $^*\dagger$ The p-values from logistic regression chi-square tests were used to compare the definitions of remission, $^*\ddagger$ Significant predictor (p<0.05); $^¥\ddagger$ RAPID3 remission could only be assessed at 13, 26 and 52 weeks; 95% CI = 95% Confidence Interval, Boolean Clinical = Boolean without CRP, CDAI = Clinical Disease Activity Index, DAS = Disease Activity Score of 44 joints, DAS28 = Disease Activity Score of 28 joints; HAQ = Health Assessment Questionnaire, RAPID3 = Routine Assessment of Patient Index Data 3, SDAI = Simplified Disease Activity Index, and SHS = Sharp - Van der Heijde Score.

TABLE 3. Predictive value of sustained remission at consecutive visits during the first treatment year for good RA prognosis during the second treatment year in early RA patients of the COBRA-light trial (n=144)

<table>
<thead>
<tr>
<th>Remission criteria</th>
<th>Good functional outcome $^\dagger$</th>
<th>Good radiographic outcome $^\ddagger$</th>
<th>Good overall outcome $^¥$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LR+  95% CI  p-value</td>
<td>LR+  95% CI  p-value</td>
<td>LR+  95% CI  p-value</td>
</tr>
<tr>
<td>Boolean</td>
<td>29.2  4.0;213.7  &lt;0.001*</td>
<td>0.6  0.2;1.7  0.35</td>
<td>4.8  1.9;12.0  &lt;0.001*</td>
</tr>
<tr>
<td>Boolean clinical</td>
<td>31.0  4.2;226.3  &lt;0.001*</td>
<td>0.7  0.3;1.8  0.44</td>
<td>5.2  2.1;12.9  &lt;0.001*</td>
</tr>
<tr>
<td>CDAI</td>
<td>6.8  3.2;14.5  &lt;0.001*</td>
<td>0.8  0.4;1.6  0.58</td>
<td>3.1  1.7;5.6  &lt;0.001*</td>
</tr>
<tr>
<td>SDAI</td>
<td>7.0  3.3;15.0  &lt;0.001*</td>
<td>0.7  0.4;1.4  0.35</td>
<td>3.3  1.9;5.8  &lt;0.001*</td>
</tr>
<tr>
<td>DAS</td>
<td>2.4  1.7;3.5  &lt;0.001*</td>
<td>1.0  0.6;1.6  0.96</td>
<td>2.1  1.5;2.9  &lt;0.001*</td>
</tr>
<tr>
<td>DAS28</td>
<td>1.8  1.4;2.4  &lt;0.001*</td>
<td>1.3  0.8;1.9  0.20</td>
<td>1.8  1.4;2.2  &lt;0.001*</td>
</tr>
<tr>
<td>RAPID3 $^§$</td>
<td>12.8  4.0;40.7  &lt;0.001*</td>
<td>1.0  0.4;2.5  0.99</td>
<td>5.2  2.4;11.2  &lt;0.001*</td>
</tr>
</tbody>
</table>

$^\dagger$ Good functional outcome = $\Delta$HAQ≤0 and HAQ consistently ≤0.5 between 52 and 104 weeks; $^\ddagger$ Good radiographic outcome = $\Delta$SHS≤0 between 52 and 104 weeks; $^¥$ Good overall outcome = good functional and good radiographic outcome between 52 and 104 weeks.

Positive likelihood ratios were calculated to compare the proportion of patients having the good outcome whose RA was at least once in sustained remission to the proportion of patients having the good outcome whose RA was never in sustained remission at 13+26, 26+39, or 39+52 weeks; $^*\dagger$ The p-values from logistic regression chi-square tests were used to compare the definitions of remission, $^*\ddagger$ Significant predictor (p<0.05); $^¥\ddagger$ RAPID3 remission could only be assessed at 13+26 and 26+52 weeks; 95% CI = 95% Confidence Interval, Boolean Clinical = Boolean without CRP, CDAI = Clinical Disease Activity Index, DAS = Disease Activity Score of 44 joints, DAS28 = Disease Activity Score of 28 joints; HAQ = Health Assessment Questionnaire, RAPID3 = Routine Assessment of Patient Index Data 3, SDAI = Simplified Disease Activity Index, and SHS = Sharp - Van der Heijde Score.
Discussion
To our knowledge, this is the first study that validates the ACR/EULAR and other remission criteria for short and sustained periods in a cohort of early RA patients. We demonstrated that early RA patients who are in remission according to any definition are likely to retain good physical function in the subsequent year; being in remission according to a strict definition, and being in sustained remission both resulted in a higher likelihood of good functional outcome. In contrast, in the context of low overall damage progression, remission did not result in a higher likelihood of good radiographic outcome.

Remission according to the fully patient-reported RAPID3 instrument has been shown to be as stringent as the ACR/EULAR criteria, and sustained RAPID3 remission showed high LRs for good functional outcome, comparable with ACR/EULAR criteria. This reinforces the utility of the RAPID3 as an instrument fit for use in busy clinical settings.

Our findings are in agreement with the literature. The 2-year results of the Finnish Rheumatoid Arthritis Combination Therapy (FIN-RACO) trial described in the article by Makinen et al demonstrated that patients in sustained remission according to the modified ACR and DAS28 criteria showed less radiologic progression than patients who were in remission at one single visit. Moreover, in the two-year results of the PREMIER trial, Aletaha et al demonstrated that sustained SDAI remission was associated with a virtual arrest of joint damage, irrespective of type of treatment. This highlights the need to not only to aim for remission, but strive to maintain it as long as possible.

The methods of our study were based on those used in the development of the ACR/EULAR remission criteria. However, our study population comprised early RA patients with no or limited damage, whereas the ACR/EULAR remission criteria were developed and validated in datasets of patients with mostly established RA and associated radiographic damage. Nonetheless, the trends in size and order of LRs are similar.

Other strengths of our study include the prospective design and trial setting: all patients included in the COBRA-light trial had recent-onset RA and had active disease at start of treatment; there were no patients in remission at baseline and all patients were treated according to the COBRA or COBRA-light protocol, including regular study visits at which remission was systematically assessed. In addition, data was available to calculate all commonly used remission criteria, which gives an unique overview of the longitudinal performance of different definitions in an early disease setting. Moreover, this is the first study that validated sustained periods of remission as predictor of good RA outcome, rather than remission at one point in time, using the methodology of the ACR/EULAR committee.

A limitation of our study and that of any longitudinal study is missing data. We therefore adopted both a realistic as well as a conservative imputation technique and showed that these imputations did not have any impact on the results yet increased the power of the analyses. Another limitation might be the lack of a wide range of radiologic
progression, which made our dataset less suitable for prediction of damage. However, this is the current situation in most early RA patients on modern treatment,\textsuperscript{4,21,33-35} so we posit that damage progression has become less important as factor for outcome in the first few years of disease. Further studies are needed to decide what degree of small radiologic progression may have clinical relevance for long-term outcomes.

At this moment, several definitions and time frames of sustained remission are used, ranging from ‘two consecutive visits, at least 1 month apart,’\textsuperscript{36} to biannual,\textsuperscript{13,37} annual,\textsuperscript{35,38,39} or even longer periods between assessments.\textsuperscript{40-43} Consensus is needed on the minimum period of remission that can be considered as clinically relevant, to form a single, uniform definition of sustained remission. Taking into account feasibility of frequent measurements, three months might be a good starting point as a minimum time frame, as demonstrated in this study.

In conclusion, in early RA remission is associated with good functional outcome in the subsequent year, with higher likelihoods on sustained remission by strict criteria. In contrast, in the context of low overall damage progression, remission did not result in a higher likelihood of good radiographic outcome. To interpret and compare future (validation) studies on sustained remission, a single, uniform definition of sustained remission is needed.
Author contributions
All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Ms Konijn had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study conception and design: Konijn, van Tuyl, Boers, den Uyl, ter Wee, Kerstens, Voskuyl, Schaardenburg, Nurmohamed, Lems. Acquisition of data: Konijn, van Tuyl, Boers, den Uyl, ter Wee, Kerstens, Voskuyl, Schaardenburg, Nurmohamed, Lems. Analysis and interpretation of data: Konijn, van Tuyl, Boers, Lems.

Role of the study sponsor
Pfizer and Dutch Top Institute Pharma had no role in the study design or in the collection, analysis, or interpretation of the data, the writing of the manuscript, or the decision to submit the manuscript for publication. Publication of this article was not contingent upon approval by Pfizer and by Dutch Top Institute Pharma.
Chapter 3

References


Chapter 3


Validation of remission criteria in early RA