34. Landewé RB, van der Heijde DM, van der Linden Sj et al. Twenty-eight-joint counts invalidate the DAS28 remission definition owing to the omission of the lower extremity joints: a comparison with the original DAS remission. Ann Rheum Dis 2006;65:637-41.
Chapter 2.2

IgM-Rheumatoid Factor and Anti-Cyclic Citrullinated Peptide Decrease by 50% During Intensive Treatment in Early Rheumatoid Arthritis

Lilian HD van Tuyl \textsuperscript{1,2}
Willem F Lems \textsuperscript{2}
Alexandre E Voskuyl \textsuperscript{2}
Pit JSM Kerstens \textsuperscript{3}
Ben AC Dijkmans \textsuperscript{3}
Maarten Boers \textsuperscript{1,2}

\textsuperscript{1} Department of Epidemiology & Biostatistics
\textsuperscript{2} Department of Rheumatology
\textsuperscript{3} VU university medical center, Amsterdam, The Netherlands
Jan van Breemen Institute, Amsterdam, The Netherlands

Ann Rheum Dis 2009 In press (in revised form)
Chapter 2.2

ABSTRACT

OBJECTIVE
To document the effect of a new tight control disease modifying antirheumatic drug treatment on IgM rheumatoid factor (IgM-RF) and anti-cyclic citrullinated peptide (anti-CCP) antibodies in early rheumatoid arthritis (RA).

METHODS
In a pilot trial of monitoring strategies, 21 patients with active early RA (mean DAS28 5.3; mean disease duration 3 months) were treated with COBRA therapy comprising sulfasalazine, methotrexate and high dose step-down prednisolone, intensified by adding hydroxychloroquine and continued low dose prednisolone. In addition, based on monitoring results, treatment adjustments were possible with methotrexate intensification after 8 or 21 weeks; and with infliximab after 21 weeks. Serum was available for 18 out of 21 patients, and was tested for anti-CCP antibodies and IgM-RF regularly up to week 40.

RESULTS
Fourteen patients were anti-CCP positive and thirteen were RF positive. Within 4 to 8 weeks, levels of both antibodies decreased by more than 50%, persisting until week 40 (p<0.05). For RF, 46% seroconverted to negative (maintained in 38%). For anti-CCP only 1 patient seroconverted. As previously reported, 90% of patients was in DAS28 remission at 40 weeks.

CONCLUSION
Remittive therapy leads to rapid and extensive decreases in antibody levels, including anti-CCP.
INTRODUCTION
Decreases of rheumatoid factor (IgM-RF) serum levels during antirheumatic treatment with disease modifying therapies\textsuperscript{1-3} and TNFα\textsuperscript{4-6} suggest IgM-RF could be useful as a monitor of response. The course of anti-cyclic citrullinated peptide (anti-CCP) in serum during treatment is less conclusive than that of IgM-RF, with some studies showing decreases\textsuperscript{3,7,8}, but others finding no change\textsuperscript{5,9-11}. For instance, Vis et al have recently shown that treatment of rheumatoid arthritis (RA) patients with the TNF blocking agent infliximab was associated with a decrease in serum levels of IgM-RF by 65%, whereas anti-CCP decreased by only 25\%\textsuperscript{11}. In contrast, Mikuls and colleagues showed a marked decline of anti-CCP levels in RA patients receiving active DMARD treatment, most profoundly in patients with a short disease duration as compared to those with established disease\textsuperscript{3}. As anti-CCP antibodies are very specific as a marker for RA\textsuperscript{12}, and are suspected to play a role in the pathology of RA, it might be important to find a therapeautic intervention that effectively decreases the levels of anti-CCP in serum of early RA patients.

The current study documents changes of 50\% or more in both IgM-RF and anti-CCP during a novel tight control treatment that starts with conventional disease modifying drugs in a modified COBRA scheme, but allows intensification to infliximab after 22 weeks. This scheme resulted in over 90\% DAS28-remission in our pilot trial\textsuperscript{13}.

METHODS
Patients and intervention
The primary object of this randomized controlled pilot study was to investigate the feasibility of disease activity monitoring with either DAS scores or urinary excretion of CTX-II. Twenty-one patients with active (DAS28>3.2), early (<36 months) RA according to American College of Rheumatology (ACR) criteria were included; all were treated for 21 weeks with intensive conventional DMARD therapy, comprising hydroxychloroquine (400 mg/d), sulfasalazine (2 g/d), methotrexate (10 mg/wk) and tapered high dose prednisolone (60 mg (wk 1); 40 mg (wk 2); 30 mg (wk 3); 20 mg (wk 4); 15 mg (wk 5); 10 mg (wk 6); 7.5 mg (thereafter))\textsuperscript{13}. Nonresponse was defined by a DAS28 > 3.2 in the DAS-group and urinary CTX-II >150 in the CTX-group. On nonresponse at 8 weeks, MTX was intensified in 2 weeks to 25 mg/wk; on nonresponse at 21 weeks, infliximab was offered to patients on high dose MTX, and MTX was intensified in the remainder. Serum was available for 18 out of 21 patients. The protocol ended after 40 weeks.

The study protocol was approved by the medical ethical committee of the Jan van Breemen Institute. The patients were informed in detail about the potential side effects of all drugs; all patients gave written informed consent.

Measurements
IgM-RF and anti-CCP were measured and analyzed at baseline and weeks 4, 8, 14, 21, 28, 32, 36 and 40. IgM-RF was measured by an in-house ELISA, and was considered positive at a cut-off level of >30 IU/ml. Anti-CCP was measured using the anti-CCP-2 ELISA according to the manufacturer’s specifications (Axis Shield) and was considered positive at a cut-off level of >5 AU/ml.

Analysis
The distributions of IgM-RF and anti-CCP were positively skewed; Wilcoxon’s signed rank test was used to determine whether the change of IgM-RF and anti-CCP at the different time points differed significantly from the baseline level.
RESULTS
All patients had early and active disease, with a mean disease duration between diagnosis and inclusion of 3 months and a mean DAS28 (SD) of 5.2 (0.9). The mean age of the 18 participants was 52 (range: 29-76) years; 72% were women.

At baseline, 5 out of 18 (30%) patients were IgM-RF negative and 4 out of 18 (22%) patients were anti-CCP negative. This resulted in available data for 13 patients for the IgM-RF analysis and 14 patients for the anti-CCP analysis. One patient dropped out at 28 weeks to work abroad; she was anti-CCP and IgM-RF positive at baseline, but both negative at 21 weeks; she was also in DAS28 remission at 21 weeks. Given the reason for drop-out, the data of this patient at 21 weeks were carried forwards to 40 weeks.

IgM-RF values decreased immediately by mean 58% in the first 8 weeks during prednisolone treatment and by 63% after 40 weeks controlled treatment. Of these 13 patients, 8 received MTX intensification at 8 weeks and subsequently 4 received anti-TNF at 21 weeks. 77% of patients (10 out of 13) experienced a ≥ 50% reduction in IgM-RF after 40 weeks of controlled treatment. For none of these patients IgM-RF antibody levels increased. Of the 5 IgM-RF negative patients at baseline, 4 decreased their RF levels (with mean 8 IU/ml from 18 to 10) and 1 increased (with 2 IU/ml from 5 to 7).

Similarly, anti-CCP antibody levels decreased by 46% in the first 8 weeks and by 48% after 40 weeks of treatment (see Figure 1). Of these 14 patients, 9 received MTX intensification at 8 weeks and subsequently 5 received anti-TNF at 21 weeks. After 40 weeks of controlled treatment, 86% of patients (12 out of 14) experienced a ≥ 50% reduction in anti-CCP antibodies. For two patients, anti-CCP antibody levels increased during 40 weeks of treatment with respectively 170% (from 370 to 1000) and 76% (from 123 to 30); these two patients showed a decrease in IgM-RF of 17% (from 634 to 529) and 76% (from 123 to 30) and they both achieved DAS28 remission. The 4 anti-CCP negative patients at baseline remained negative without a change in levels of antibodies and all achieved DAS28 remission.

Table 1 shows that the changes of DAS28, IgM-RF and anti-CCP from baseline are significant at every time point (p<0.05).
At 8 weeks, 6 out of 13 (46%) IgM-RF positive patients turned IgM-RF negative; at 40 weeks, five out of 13 (38%) remained IgM-RF negative while 1 patient turned positive again. Only one out of 14 anti-CCP positive patients turned negative at 21 weeks.

Table 1  DAS28, IgM-RF and anti-CCP during 40 weeks of intensive treatment for all 18 patients

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>8 weeks</th>
<th>21 weeks</th>
<th>40 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DAS28</strong></td>
<td>5.2(0.9)-</td>
<td>2.3(1.3)-</td>
<td>2.2(1.4)-</td>
<td>1.5(0.9)-</td>
</tr>
<tr>
<td><strong>IgM-RF (U/ml)</strong></td>
<td>5.2(3.9-7.3)</td>
<td>2.4(0.5-4.1)</td>
<td>2.0(0-5,2)</td>
<td>1.4(0-3.6)</td>
</tr>
<tr>
<td><strong>Anti-CCP (U/ml)</strong></td>
<td>49(5-634)</td>
<td>24(4-443)</td>
<td>15(3-340)</td>
<td>15(7-529)</td>
</tr>
</tbody>
</table>

Mean (SD)-median (range)

* Significantly different from baseline (p<0.05) calculated using Wilcoxon’s signed rank test
**Figure 1** Upper panel: Percentage change of anti-CCP from baseline for all anti-CCP positive patients; the light grey fat line represents the mean percentage decrease of anti-CCP for all anti-CCP positive patients. Lower panel: all patients received the original COBRA schedule (black), intensified by the addition of hydroxychloroquine, methotrexate 10 mg instead of 7.5 mg and continuation of low-dose prednisolone instead of tapering after 28 weeks (dark grey). Decisions to intensify methotrexate and to start infliximab infusions (light grey) were based on monitoring results.
DISCUSSION
This pilot study suggests that intensive conventional DMARD therapy with initial high dose prednisolone according to the COBRA schedule can rapidly decrease both IgM-RF and anti-CCP serum levels in early RA patients, although for anti-CCP sero-conversion rarely occurs. Rapid decreases in RF have also been documented in the original COBRA trial\textsuperscript{14} and other studies\textsuperscript{1-6,15} but to our knowledge, such profound decreases of anti-CCP during treatment of early RA patients have not been described before. Most comparable are the results of Mikuls et al, who reported on patients receiving active DMARD treatment; 52% achieved a $\geq 25\%$ reduction in the anti-CCP antibody levels and 33% achieved a $\geq 50\%$ reduction. Decrease was most profound in patients with a short disease duration. In our study, one patient had a disease duration of 19 months, the others were all below 8 months. This one patient dropped out of the study after 28 weeks, but had turned both RF and anti-CCP negative within 21 weeks from start of the treatment. The presence of rheumatoid factor and anti-CCP antibody in early disease is associated with more severe disease and rapid radiologic progression\textsuperscript{16,17}. It has been suggested that anti-CCP antibodies have a pathogenic role in the development of RA, because of their high disease specificity and frequent presence in early disease. If so, monitoring anti-CCP levels alongside disease activity might increase the efficacy of treatment strategies aimed at preventing damage and disability. Our observations can only be viewed as preliminary given the small sample size and the primary study question. Nevertheless, they strengthen the suggestion that intensive conventional treatment including initial high oral prednisolone, and infliximab add-on where necessary, can lead to new levels of disease control in early RA.

ACKNOWLEDGMENT
The authors thank Anke van Rees, Jan van Breemen Institute for her large contribution to the conduct of this study. This study was supported by an unrestricted research grant from Schering Plough BV.
REFERENCES


Chapter 3.1

Defining remission in rheumatoid arthritis: results of an initial ACR/ EULAR consensus conference

Lilian HD van Tuyl 1
Steven C Vlad 2
David T Felson 2
George Wells 3
Maarten Boers 1
for the ACR ad hoc committee to define remission for clinical trials.

1 Department of Epidemiology & Biostatistics and Department of Rheumatology, VU University Medical Center, Amsterdam, The Netherlands
2 Clinical Epidemiology Research and Training Unit, Boston University School of Medicine, Boston, USA
3 Department of Epidemiology and Community Medicine, University of Ottawa, Ottawa, Canada
* Co-principal authors
ABSTRACT

OBJECTIVE
Due to advances in therapies for rheumatoid arthritis (RA) over the last years, an increasing proportion of patients are able to achieve a state of ‘remission’. But what exactly is remission? At the moment, randomized controlled trials around the world use different remission definitions and consequently measure different aspects of a patient’s disease state. For research findings to be correctly interpreted, the need for a uniform definition of remission is vital.

METHODS
The American College of Rheumatology (ACR) constituted a committee to redefine remission in RA that included international clinical researchers, trialists and clinical epidemiologists. This group was asked to study current definitions of remission, explore the theoretical underpinning of the concept of ‘remission’, and develop a research agenda that would inform future work in the development of an ACR definition of remission.

RESULTS
In its first meeting, the committee preferred to develop a ‘strict’ definition, implying no or very low disease activity. Such a definition would need to be validated against long-term outcome e.g. physical function and damage.

CONCLUSION
The committee decided to consider both a definition for trials and a modified version for clinical practice.
Since the first meeting, the ACR and the European League Against Rheumatism (EULAR) have decided to sponsor this initiative as an official ACR/EULAR collaboration.
INTRODUCTION
The current ACR definition of clinical remission for rheumatoid arthritis (RA) (Preliminary ARA Criteria for Clinical Remission), was published in 1981 (Table 1).

### Table 1  ACR Preliminary Criteria for Remission of Rheumatoid Arthritis

<table>
<thead>
<tr>
<th>criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Morning stiffness not to exceed 15 minutes</td>
</tr>
<tr>
<td>2. No fatigue</td>
</tr>
<tr>
<td>3. No joint pain</td>
</tr>
<tr>
<td>4. No joint tenderness or pain on motion</td>
</tr>
<tr>
<td>5. No soft tissue swelling in joints or tendon sheaths</td>
</tr>
<tr>
<td>6. ESR (Westergren method) less than 30mm/h (females) or 20mm/hr (males)</td>
</tr>
</tbody>
</table>

Exclusions prohibiting a designation for complete clinical remission: clinical manifestations of vasculitis, pericarditis, pleuritis, myositis, unexplained recent weight loss or fever secondary to RA

At the time of this development relatively few patients achieved remission, in part because there were few highly effective treatments for disease. Since this time, randomized controlled trials have focused on whether drugs could be shown to improve disease, prompting the development and widespread use of a single core set of endpoints for trials (WHO-ILAR core set)², and validated measures of disease improvement (ACR20, EULAR criteria). At the time of its development, showing a significant ACR20 improvement compared to placebo represented a significant advance in improving disease outcomes³,⁴. With the evolution of more effective treatments for RA, these improvement measures have been stretched. RA trials now routinely use ACR50, ACR70 and sometimes even ACR90 responses as secondary outcomes, and increasing numbers of trial subjects achieve these endpoints⁵-⁷. Within the Outcome Measures in Rheumatology Clinical Trials (OMERACT) initiative, the importance of achieving an acceptable state of low disease activity has resulted in a preliminary definition of what is termed ‘minimal disease activity’⁸. With emerging new treatment strategies, developments are rapid, and trials where remission is the primary outcome are becoming more and more prevalent⁹-¹¹.

However, there are problems with the current definitions of remission. While the ACR remission criteria might be used to characterize persons attaining remission, they are problematic, since they are so restrictive that few patients, even in current trials attain this state¹². Further, they include measures not in the core set (fatigue, morning stiffness; tendon sheath swelling) and others that are not always routinely assessed in trials (ESR). To account for some of these issues, modified ACR criteria (mACR) have been employed where fatigue is omitted and the presence of 4 of the remaining 5 items is required¹³,¹⁴. Amongst all disease activity scoring systems that are available today, the most commonly used measures for remission are based on the Disease Activity Score (DAS). A (full joint count) DAS < 1.6 correlates well with the ACR remission criteria¹⁵, but it is the 28-joint count DAS (DAS28) that is currently most commonly used. A DAS28 with a cut-off point of 2.6 corresponded best to the fulfilment of the modified ACR criteria for clinical remission, which means that patients who meet the modified ACR remission criteria will meet the DAS28 cut-off (although because the DAS cut-off is less stringent, those who meet DAS cut-off will not necessarily meet modified ACR remission criteria)¹³. However, a DAS < 1.6 may constitute a more stringent measure of remission than DAS28 < 2.6¹⁶. Indeed it has been reported that up to 20% of patients in DAS28 remission have 2 or more residual swollen joints, and the number of swollen joints can reach more than a dozen¹⁷-²⁰. These findings suggest that patients in DAS28 remission may actually be in a ‘minimal disease activity state’ rather than in true remission⁸. However, also in DAS remission there can be a considerable number of...
swollen joints. Further, in recent clinical trials DAS28 remission rates exceeded those of ACR70 response rates, meaning that more patients achieved a state of DAS28 remission than the proportion of patients reaching a 70% or higher decrease in tender and swollen joints. Since neither the ACR remission criteria nor the full DAS definition is often used and the DAS28 may not be stringent enough to define true remission, there appears to be a need for an easy to use definition that is suitable as either a secondary or primary outcome in clinical trials.

Given these concerns, the ACR constituted a committee joint by EULAR representation, to redefine remission in RA. This group met initially in November 2007, and consisted of an international group of rheumatoid arthritis (RA) clinical researchers, trialists and clinical epidemiologists. Their charge was to study current definitions of remission, explore the theoretical underpinning of the concept of ‘remission’, and develop a research agenda that would inform future work in the development of an ‘authorized’ ACR clinical trial definition. This document summarizes their considerations, conclusions and research agenda for the coming period and aims to give readers insight into the complexity of the process by raising many questions that have to be taken into account.

METHODS
Meeting Format
The format of the meeting is shown in Table 2. Three presentations were given by the committee chairpersons to clarify the issues involved. The whole group was then divided into three breakout groups, each charged with exploring a series of questions concerning remission: (1) conceptual issues, (2) measurement issues or (3) potential setting and uses (Table 2). Members of each group were encouraged to develop additional questions in their areas.

Presentations
Basic Concepts of Remission and Current Definitions (Maarten Boers)
Dr. Boers began the meeting by reminding the group of the “OMERACT filter”, that requires that measures used should be truthful, discriminative, and feasible in their intended setting. He expanded on this core definition, suggesting that being truthful implied that the definition was free from bias and relevant, that discriminative implied that the definition could distinguish between states reliably and reproducibly at multiple time points and was sensitive to change, and that feasibility applied to time for implementation of the definition, cost of use, and ease of interpretability.

He then presented the concept that remission could be defined as absence of disease activity, but with the possibility that disease could return in time. In this way it was to be distinguished from a ‘cure’ or ‘arrest’ of the disease. In this concept, remission is a state, not a change or a transition between states. In his opinion, the concept of remission is independent of the time spent in the state, although time may be of use in defining a sustained state of remission. He asked the group to consider how one could be sure that RA disease activity was absent and suggested that the definition of remission could change depending on the setting (trial vs. clinic).

Turning to current definitions of remission, he reviewed Pinals’ 1981 definition of remission (Table 1) and other definitions including:

1. DAS < 1.6 or DAS28 < 2.6. These are commonly used definitions (esp. the DAS28) and researchers in Nijmegen, The Netherlands have validated these against a less stringent version of preliminary ARA criteria for clinical remission (also called the...
Defining Remission in Rheumatoid Arthritis

mACR criteria defined as 4 out of 5 criteria from which fatigue was omitted and for a period of 3 months)\(^{13}\).

2. The simplified disease activity index (SDAI) \(\leq 3.3\) and the clinical disease activity index (CDAI) \(\leq 2.8\). These two definitions use almost the same variables as the DAS28 (i.e. swollen and tender joint counts and the patient global assessment) but in addition they include physician global assessment which is not included in the DAS28, and CRP (in SDAI but not in CDAI) which is used in a modified DAS28 (otherwise ESR is used). For the SDAI and CDAI, these variables are summed into one total score\(^{17}\). By virtue of their formula, in a state of remission 2 swollen or 2 tender joints, or 1 of each, cannot be exceeded.

3. The patient activity scale (PAS) \(\leq 1.25\) and the routine assessment of patient index data version 3 (RAPID3) score \(\leq 1\).\(^{24}\) These are similar, patient-derived measures consisting of different weighted combinations of function, pain, and patient global assessment. They were not designed for trials, but rather are meant for clinical use\(^{25}\).

Evaluation of these definitions in large cross-sectional studies\(^{14,26,27}\) suggest that they can roughly be categorised as either ‘strict’ (ACR, CDAI/SDAI, PAS/RAPID3) or ‘lax’ (the mACR criteria and the DAS28 definition), with the latter being very similar to the OMERACT definition for minimal disease activity (MDA)\(^{8}\); MDA is a different, though related concept than that of remission because by definition, everyone in remission will also be in MDA. During the OMERACT 6 and 7 meetings, participants agreed to a preliminary MDA definition: a decision node places all patients without tender and swollen joints and an ESR <10 in MDA; furthermore, patients with either a DAS28 \(\leq 2.85\) or meeting 5 out of 7 core set criteria were placed in MDA\(^{28,29}\).

Besides the unfavourable situation that different proportions of patients are classified as MDA or remission depending on the definition that is used\(^{20,31}\), there are also aspects of feasibility and acceptability to patients and health professionals that should be taken into account\(^{26,32}\):

How much time/effort does it take to obtain a complete measure of remission? What is an acceptable burden for patients in obtaining a measure of remission?

**Issue of Validity in Defining Remission in RA (David Felson)**

Dr. Felson suggested that a definition or measurement should have ‘content validity’, i.e. it should represent all facets of a concept. With content validity in mind, he challenged the group to consider what elements would be required for a definition of remission by presenting the following questions:

1. Is a definition based on a 28 joint count (such as the DAS28 and SDAI/CDAI) sufficient to define remission? Would this be acceptable if joints in the feet (not assessed in the 28 joint count) were active?
2. Should a definition use only measures from the ACR core set (tender and swollen joint counts, patient and physician global assessment, function, pain, and ESR/CRP), or would additional measurements (e.g. fatigue) be needed?
3. What role does morning stiffness and/or fatigue play in defining remission?
4. What role does imaging play? Should ‘remission’ imply a lack of radiographic or MRI progression over time? What if measures of ‘clinical’ and ‘radiographic’ remission do not agree in a single subject?
5. How should changes due to chronic disease be incorporated (or not incorporated) into a remission definition?
6. Does time play a role in a definition of remission?
   - Should remission at one time predict remission at all future times?
   - What if a patient is in ‘remission’ at one clinic visit but not the following one? Has that subject achieved remission?
7. Should remission have predictive validity? That is, should it predict outcomes such as joint damage, disability, and death?

**Issues of Discrimination in Definitions of Remission in RA (George Wells)**

Discrimination implies that a measurement is able to distinguish between different states that are of interest at a certain time point and on different time points, in a reliable, reproducibly and sensitive way. Using actual data from a group of randomized controlled trials, Dr Wells conducted preliminary studies to determine how current definitions of remission discriminate between placebo and active treatment (either DMARDs or biologic agents) in trials. A number of definitions did this well, including the DAS, physician global, and PAS II. Also of note, remission rates varied markedly depending on the remission definition, with the DAS28 and PAS II giving the highest rates of remission and the SDAI, CDAI and ACR criteria giving the lowest.

These factors will be important for the issue of feasibility. The sample size necessary in a trial depends on the discriminative ability of a measure. At a given level of alpha (probability of a type I error) and beta (probability of a type II error) the better the discrimination of a measure then the smaller the number of subjects needed to show a significant difference between control and active medication.

**Table 2** Structure of the ACR/EULAR remission workshop

<table>
<thead>
<tr>
<th>Session type</th>
<th>Content</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presentations</td>
<td>- Basic Concepts of Remission and Current Definitions (Maarten Boers)</td>
</tr>
<tr>
<td></td>
<td>- Issue of Validity in Defining Remission (David Felson)</td>
</tr>
<tr>
<td></td>
<td>- Issues of Discrimination in Definitions of Remission (George Wells)</td>
</tr>
<tr>
<td>Breakout groups</td>
<td>1) Conceptual issues</td>
</tr>
<tr>
<td></td>
<td>- Should remission be defined as an absence of disease activity or as</td>
</tr>
<tr>
<td></td>
<td>minimal disease activity?</td>
</tr>
<tr>
<td></td>
<td>- Should long term outcomes be included?</td>
</tr>
<tr>
<td></td>
<td>- Should remission be defined only as remission off anti-rheumatic</td>
</tr>
<tr>
<td></td>
<td>treatment or regardless of anti-rheumatic treatment?</td>
</tr>
<tr>
<td></td>
<td>2) Measurement issues</td>
</tr>
<tr>
<td></td>
<td>- What variables should be included?</td>
</tr>
<tr>
<td></td>
<td>- Should we use limited joint counts or only full joint counts?</td>
</tr>
<tr>
<td></td>
<td>- Should duration of state be incorporated?</td>
</tr>
<tr>
<td></td>
<td>- Should we focus on particular remission definitions currently</td>
</tr>
<tr>
<td></td>
<td>proposed or variations on them?</td>
</tr>
<tr>
<td></td>
<td>3) Potential setting and uses</td>
</tr>
<tr>
<td></td>
<td>- Do we also need to define remission for practice settings?</td>
</tr>
<tr>
<td></td>
<td>- Should trial and practice based definitions be related?</td>
</tr>
<tr>
<td></td>
<td>- Should remission be used as a primary or secondary outcome in</td>
</tr>
<tr>
<td></td>
<td>trials?</td>
</tr>
<tr>
<td></td>
<td>- What other not yet validated measures of disease activity should</td>
</tr>
<tr>
<td></td>
<td>be considered for inclusion in future definitions of remission?</td>
</tr>
</tbody>
</table>

**Presentations of results and discussion**

**Plenary**

Summary

Overview of research agenda
RESULTS FROM BREAKOUT GROUPS

The following results (Table 3) are based on the feedback from the three breakout groups and the subsequent plenary session.

**Topic 1: Conceptual issues related to the definition of remission**

*Should remission be defined as an absence of disease activity or as minimal disease activity?*

There was unanimous agreement on the need for a strict definition of remission with stringent criteria (to differentiate remission from low disease activity). These criteria should include: (1) no clinical disease (although the participants acknowledged that an absence of disease activity and of / pain may not always be possible); and (2) lack of progression over time. It would be wise to create a separate remission definition with a similar structure as used for the minimal disease activity definition. The group also felt it was important to continue to work separately on the validation of a minimal disease activity definition in relation to the new remission definition.

*Should long term outcomes be included?*

It was felt that the definition of remission should be independent of long term outcomes such as radiographic damage, but that the validity of the definition should be tested using x-ray / ultrasonography / MRI damage indices and HAQ function. Those in remission should have no/reduced progression of joint damage and should have less deterioration or more improvement in functional status (using HAQ) over time (remission definition should have predictive validity). However, the definition of remission should be based largely on clinical and biochemical parameters at this stage, and not include definitions that require imaging. It was felt that at present there is not enough data on the use of imaging such as ultrasonography and MRI in this field to formulate a precise imaging based definition of remission but that this is an important area for future research.

*Should treatment be part of the definition?*

All agreed that therapy should not be a part of the definition of remission.

**Other conceptual issues**

One question concerned the best cut-off points for each current definition that predicts lack of damage progression. Can we explore existing data to find the best cut-off points?

**Topic 2: Measurement issues**

*What variables should be included?*

The three most important variables were felt to be: (1) tender joint count, (2) swollen joint count and (3) an acute phase reactant. For all other possible variables it was felt that more data are needed; first with a focus on pain (for example, how should one deal with non-RA pain?), and then focusing on fatigue, physician global assessment (utility of continuous vs dichotomous scale), patient global assessment, sleep, and the HAQ.

*Should we use limited joint counts or full joint counts?*

It was felt that while a 28 joint count may be sufficient to assess disease activity, more joints should be included if a stringent remission definition is desirable. Further data were felt to be needed about how many patients in a DAS28 remission state still have activity in non DAS28 joints. Based on these data, it should then be decided whether this is an important issue (in trials the issue may be less important than in clinical practice). With current knowledge, most attendants felt that a 28-joint count was not sufficient for the purpose of developing a stringent definition of remission.
Should duration of state of remission be incorporated?
The group felt that sustained remission was a critical outcome but that time was not necessarily a part of the trial definition of remission (although it might be a secondary outcome). Some felt that it would be valuable to ask patients about their perception of the importance of ‘time in remission’. The patient-attendee stressed the importance of time for her in the definition of remission: she saw it as a permanent state, from which there should be no recurrence of disease, especially not within a limited time. The relevance of time was also discussed in the light of damage progression: Can we calculate what period of time in remission is needed so as not to see any future damage progression?

Should we focus on particular remission definitions currently proposed or variations on them?
No conclusion was reached on this topic. There is a need to collect prospective data including a wide range of variables to make sure we are not locked into previous decisions about what variables to include.

Topic 3: Potential setting and uses
Do we also need to define remission for practice settings?
All participants agreed that there should also be a remission definition for clinical practice. Trials differ from clinical practice in aspects such as restricted time, measures that lead to additional health care cost, patient characteristics that differ from those in clinical trials, and physicians’ needs. These differences may result in different definitions of remission in trial versus practice settings. A patient based measure could be developed for this environment.

Should trial and practice based definitions be related?
The trial definition should be closely linked with the practice definition, taking into account clinical trials’ need for accuracy, and the need for feasibility and cost in clinical practice. A trial definition should maximize the efficiency of the trial while a modified or lower efficiency version might be used in clinical practice.

Should remission be used as a primary or secondary outcome in trials?
The needs of a trial should determine whether remission is the primary or a secondary outcome in a study.

What other not yet validated measures of disease activity should be considered for inclusion in future definitions of remission?
No conclusion was reached.

DISCUSSION
The first ACR remission workshop concluded that a new remission definition should be strict, based on no or very low disease activity and should be validated against long-term outcome, specifically physical function and radiographic progression. Treatment should not be part of the remission definition, nor should long term absence of disease activity, although the latter could be used for validation purposes. The definition should at least include the tender and swollen joint counts, probably include non-DAS28 joints, and an acute phase reactant. Besides an efficient trial remission definition, there is also a need for a modified version for use in clinical practice. Similar work has been done by experts in the field of juvenile inflammatory arthritis (JIA), who using consensus approaches, formulated preliminary remission definitions in JIA. Similarities between the JIA definition and the RA definition are the need for stringency: the JIA criteria for a patient to qualify for inactive disease are: no joints with active arthritis; no fever, rash, serositis, spenomegaly, or generalized
lymphadenopathy attributable to JIA; normal ESR or CRP; and physician’s global assessment of 0. Important differences with the RA definition of remission are the incorporation of drug use and duration in JIA: in JIA, a patient is in remission if criteria for inactive disease are met for 6 continuous months for a patient on medication, and for 12 continuous months off medication. Unlike JIA, the construction of the RA remission definition started with expert consensus on the main elements of a new definition, but will be guided by analysis of data from clinical trials. This initial workshop has raised many important research questions that will be addressed by a research agenda and subsequent meetings of the committee to evaluate findings from the data analysis that is part of the research agenda. ACR and EULAR have decided to sponsor this initiative as an official ACR-EULAR collaboration.

Table 3  ACR/EULAR remission committee research agenda

<table>
<thead>
<tr>
<th>Conceptual issues</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assessment of reliability/reproducibility of the remission definition: consistency of remission over visits in a trial on constant treatment (or for a patient in remission at one visit some assurance that their adjacent visits show very low disease activity at most).</td>
</tr>
<tr>
<td>Predictive validity of candidate definition against X-rays and physical function.</td>
</tr>
<tr>
<td>Relationship between remission and MDA and longer term outcome (function, disability)</td>
</tr>
<tr>
<td>The role of imaging (ultrasonography and MRI) in the definition, measurement, assessment and monitoring of the remission state</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Measurement issues</th>
</tr>
</thead>
<tbody>
<tr>
<td>What disease activity measures should be included? Consider data sets where there is an independent measure of remission to test the relation of remission to disease activity measures.</td>
</tr>
<tr>
<td>What is the exact question in physician and patient globals?</td>
</tr>
<tr>
<td>What about reliability: between physician variability?</td>
</tr>
<tr>
<td>Do we need 28 joints or more? Review of literature on the likelihood of joint activity when 28 joints are 0. And when 28 joint count is zero, how many other joints are active?</td>
</tr>
<tr>
<td>Should we give priority to specific joints?</td>
</tr>
<tr>
<td>Should we ask patients if they feel they are in remission?</td>
</tr>
<tr>
<td>Duration of remission: for patients in remission at one time point, are they likely to be in remission at adjacent time points? If not, is their disease very inactive at adjacent time points? If adjacent time points show very low disease activity, then remission at one time is valid and remission probably does not need to be defined at more than one time point.</td>
</tr>
<tr>
<td>Role of imaging (ultrasonography and MRI)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Potential setting and uses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Are there equivalent measures, easier to use in practice, which give the same information?</td>
</tr>
<tr>
<td>Could we reduce the number of measures for the practical setting, but still resemble the same remission criterion?</td>
</tr>
</tbody>
</table>
APPENDIX  List of members of the ad-hoc committee to define remission in RA

Members of the *ad hoc* committee, in addition to the authors, were:

- **Daniel Aletaha**, Medical University Vienna, Austria
- **Claire Bombardier**, University of Toronto & Mount Sinai Hospital, Toronto, Canada
- **Stefano Bombardieri**, University of Pisa, Italy
- **Peter Brooks**, University of Queensland, Brisbane, Australia
- **Andrew K Brown**, Hull & York Medical School, University of York; York Hospital Foundation Trust, United Kingdom
- **Hyon K Choi**, University of British Columbia, Arthritis Research Center of Canada, Vancouver, Canada
- **Bernard Combe**, Hopital Lapeyronie CHU Montpellier, Université Montpellier, France
- **Maxime Dougados**, Hopital Cochin, Service de Rhumatologie B, Paris, France
- **Paul Emery**, Leeds Institute of Molecular Medicine, University of Leeds, Leeds Teaching Hospitals Trust, Chapel Allerton Hospital, United Kingdom
- **Daniel E Furst**, Geffen School of Medicine, University of California, Los Angeles, USA
- **Juan J Gomez-Reino**, Hospital Clinico Universitario Santiago, Spain
- **Gillian Hawker**, Women’s College Hospital, University of Toronto, Canada
- **Désirée van der Heijde**, Leiden University Medical Center, The Netherlands
- **Kent Johnson**, University of Newcastle NSW, Australia
- **Thomas Karonitsch**, Medical University of Vienna, Austria
- **Edward C Keystone**, University of Toronto, Canada
- **John Kirwan**, University of Bristol, Bristol Royal Infirmary, United Kingdom
- **Tore K Kvien**, Diakonhjemmet Hospital, University of Oslo, Norway
- **Robert BM Landewé**, Maastricht University Medical Center, The Netherlands
- **Michael LaValley**, School of Public Health, Boston University, USA
- **Joachim Listing**, German Rheumatism Research Center, Berlin, Germany
- **Emilio Martin Mola**, Hospital Universitario La Paz, Madrid, Spain
- **Marco Matucci Cerinic**, University of Florence, Italy
- **Kaleb Michaud**, University of Nebraska Medical Center, Omaha & National Data Bank for Rheumatic Diseases, Wichita, USA
- **Larry W Moreland**, University of Pittsburgh, Pittsburgh, USA
- **Harold E Paulus**, David Geffen School of Medicine, University of California, Los Angeles, USA
- **Theodore Pincus**, New York University Hospital for Joint Diseases, USA
- **Pam Richards**, University of Bristol, United Kingdom
- **Piet LCM van Riel**, Radboud University Nijmegen Medical Center, The Netherlands
- **Vibeke Strand**, Stanford University School of Medicine, Palo Alto, CA, USA
- **Tuulikki Sokka**, Jyväskylä Central Hospital, Finland
- **Lee S Simon**, Harvard Medical School, Beth Israel Deaconess Medical Center, USA
- **Peter Tugwell**, University Of Ottawa, Canada
- **Alan Tyndall**, University of Basle, Switzerland
- **Jeffrey N Siegel**, Food and Drug Administration, Silver Spring, MD, USA
- **Josef S Smolen**, Medical University of Vienna, Austria
- **E William St Clair**, Duke University Medical Center, Durham, USA
- **Ronald F van Vollenhoven**, The Karolinska Institute, Stockholm Sweden
- **Michael M Ward**, National Institutes of Health, Bethesda, MD, USA
- **Fred Wolfe**, National Data Bank for Rheumatic Diseases, Wichita, USA
- **Bin Zhang**, Boston University School of Medicine, USA
- **Angela Zink**, Charité Medical School, Berlin, Germany
REFERENCES

25. Pincus T, Amara I, Segurado OG et al. Relative efficiencies of physician/assessor global estimates and patient questionnaire measures are similar to or greater than joint counts to distinguish adalimumab from control treatments in rheumatoid arthritis clinical trials. J Rheumatol 2008; 35(2):201-205.


Chapter 3.2

Systematic review:
Evidence for Predictive Validity of Remission on Long Term Outcome in Rheumatoid Arthritis

Lilian HD van Tuyl 1
David T Felson 2
George Wells 3
Josef Smolen 4
Bin Zhang 2
Maarten Boers 1

1 Department of Epidemiology & Biostatistics and Department of Rheumatology, VU university medical center, Amsterdam, The Netherlands
2 Clinical Epidemiology Research and Training Unit, Boston University School of Medicine, Boston, USA
3 Department of Epidemiology and Community Medicine, university of Ottawa, Ottawa, Canada
4 Medical University of Vienna and Hietzing Hospital, Vienna, Austria

Submitted
ABSTRACT

OBJECTIVE
Remission is becoming a frequently used endpoint of rheumatology clinical trials, although its definition is not satisfactory. Although it is generally believed that achieving a state of remission will lead to better structural outcome, there is no systematic overview of the literature available. As a part of an undertaking to redefine remission, the current review describes the relationship between remission and long term structural outcome.

METHODS
A systematic literature search of PubMed, Embase.com, and the Cochrane Library intersected three groups of terms: rheumatoid arthritis, remission and long term outcome. The search identified 1138 records, of which 14 were relevant to the research question.

RESULTS
All the studies included in this review showed a relationship between remission and long term structural damage or disability. Patients that achieved a state remission, defined in various ways, showed less deterioration of function and radiographic progression compared to patients who did not reach a state of remission.

CONCLUSION
Patients who achieve a state of remission, are more likely to show less deterioration of function and radiographic progression compared to patients that do not reach a state of remission.
INTRODUCTION

Treatment of rheumatoid arthritis (RA) has improved substantially in the past twenty years. Although RA is a chronic disease without a known cure, a state of remission or low disease activity is achieved by a substantial number of patients participating in clinical trials\textsuperscript{1-3} and even patients in clinical practice\textsuperscript{4,5}. In the ‘quantitative patient questionnaires in standard monitoring of patients with rheumatoid arthritis’ (QUEST-RA) project, remission occurred frequently, but this depended strongly on the definition used: percentages of patients in remission varied from 9\% for the American college of Rheumatology (ACR) definition of remission to 20\% for the disease activity score in 28 joints (DAS28) definition of remission. Likewise, using the ‘care for RA database’ (CARAbase)\textsuperscript{6}, a recent study showed differences when different scores were employed, with the lowest proportions of remission observed with the simplified disease activity index (SDAI) followed by ACR remission criteria and DAS28 remission; in DAS28 remission, patients had up to 9 swollen joints, while in SDAI remission 1-2 swollen joints were seen in only 5\% of the patients\textsuperscript{7}. In fact, DAS28 remission has often been seen to exceed ACR70 response rates\textsuperscript{1,8}, and sometimes even ACR50 response rates\textsuperscript{9}, indicating significant residual disease activity in many patients in DAS28 remission. The findings of these papers highlight the need for a uniform definition of remission in RA.

In a collaborative project, ACR and the European League Against Rheumatism (EULAR) have constituted a committee to redefine remission in RA. In its first publication, the committee concluded that a new remission definition should be strict, based on no or very low disease activity and should be validated against long-term outcome, specifically physical function and radiographic progression\textsuperscript{10}. The committee agreed that the new definition of remission should be able to predict patients who achieve and remain in a state of remission, will have no or little progression of joint damage and less deterioration or more improvement in physical function. But is it possible to predict this favorable long term outcome based on a definition of remission? What is the current body of knowledge that proves that being in a state of remission for a certain period will lead to better outcomes compared to not being in remission?

This systematic review aims at collecting and reviewing all available evidence on the ability of remission (according to a certain remission definition) to predict long term outcome (ie the stability of x-ray damage or stability of physical function). In other words, what is known about the predictive validity of the currently available remission definitions?

METHODS

Every article that studied the relationship between remission (by any definition) and long term outcome in terms of function and radiological progression was included in this review.

Literature search

A systematic literature search of PubMed (on 6 October 2008; primary search), Embase.com (on 20 October 2008), and the Cochrane Library (on 5 November 2008) identified studies addressing the longitudinal relationship between any kind of remission definition and long term RA outcome. The search did not include limitations for language. Search terms included medical subject headings (MeSH) or keywords when appropriate. The search intersected three groups of terms. The first group described the disease rheumatoid arthritis, the second group described the condition of remission according to any available definition, and the third group described the concept of long term outcome in terms of function and radiological progression. To be included in the review, the population studied must be patients with RA, remission as well as long term outcome must have been defined clearly and the
measurement of remission had either to be concurrent with or precede the interval over which the long term outcome was assessed.

Two authors composed the search strategy (LvT and MB) in consultation with medical information specialists. For the exact strategy, see Table 1.

Data extraction

Titles and abstracts of citations resulting from the search were screened for relevance by LvT. This resulted in an initial set from which LvT and another independent reviewer (MB) subsequently selected the full articles to be retrieved. The same reviewers independently assessed these for final eligibility (Figure 1). Screening the references for relevant articles identified other potentially relevant articles which were subsequently retrieved and assessed. Furthermore, all members of the committee on remission were asked to review the final list of relevant articles and to identify other work (published or not) that could be relevant to the research question.

Analysis

Narrative summaries of the articles were compiled that highlighted the following characteristics: number of patients included in the study, disease duration at inclusion, the type of intervention/treatment that patients received during the study, the type of remission definition(s) used to classify patients as in or not in remission, percentage of patients achieving remission, the duration of remission, the follow up time of the study and the assessment of outcome: lower radiological progression and/or lower score on the health assessment questionnaire (HAQ).

### Table 1  Search strategies

<table>
<thead>
<tr>
<th>Search</th>
<th>Topic</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PubMed 6 October 2008</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>1</strong></td>
<td>Disease: rheumatoid arthritis</td>
<td></td>
</tr>
<tr>
<td>MeSH</td>
<td>((&quot;Arthritis, Rheumatoid&quot;[MeSH:NoExp] OR &quot;Caplan's Syndrome&quot;[MeSH]) OR &quot;Felty's Syndrome&quot;[MeSH]) OR &quot;Rheumatoid Nodule&quot;[Mesh] OR</td>
<td></td>
</tr>
<tr>
<td>Free Text</td>
<td>arthriti*[tiab] OR rheuma*[tiab] OR caplan*[tiab] OR felty*[tiab]</td>
<td>154812</td>
</tr>
<tr>
<td><strong>2</strong></td>
<td>Remission: by any definition</td>
<td></td>
</tr>
<tr>
<td>MeSH</td>
<td>(&quot;Remission Induction&quot;[MeSH] OR &quot;Remission, Spontaneous&quot;[MeSH]) OR</td>
<td></td>
</tr>
<tr>
<td>Free Text</td>
<td>remission*[tiab] OR ((absence*[tiab] OR minimal*[tiab] OR low*[tiab] OR no*[tiab]) AND (disease activit*[tiab]))</td>
<td>87877</td>
</tr>
<tr>
<td><strong>3</strong></td>
<td>Long term RA outcome: function and radiographic progression</td>
<td></td>
</tr>
<tr>
<td>MeSH</td>
<td>&quot;Health Status Indicators&quot;[MeSH] OR</td>
<td></td>
</tr>
<tr>
<td>Free Text</td>
<td>haq*[tiab] OR aims2*[tiab] OR</td>
<td></td>
</tr>
<tr>
<td><strong>4</strong></td>
<td>Combination</td>
<td></td>
</tr>
<tr>
<td></td>
<td>#1 AND #2 AND #3</td>
<td>643</td>
</tr>
</tbody>
</table>
RESULTS
The PubMed, Embase.com and Cochrane library databases identified 1138 possible articles referring to remission in rheumatoid arthritis in relation to long term outcome. Figure 1 shows how the final selection of fourteen articles was made. Searches in Embase.com and The Cochrane Library did not provide additional articles. The expert committee provided one additional article and several relevant background articles. Checking the references of all relevant articles provided two additional articles.

Of the 14 studies, five used the DAS28<2.6 remission definition; the SDAI<3.3, DAS<1.6 and a modified version of the ACR criteria were used four times, the full ACR criteria were used two times, and the following definitions were all used one time: DAS28<2.4, rheumatologists judgement, patient reported remission, time averaged DAS<1.6, DAS28<2.6 for at least 1 year, DAS28<3.2, DAS28<2.84 and CDAI<2.8. Heterogeneity was also present in outcome measures. Table 2 presents specific details and sources of heterogeneity of all articles included in the review.

All studies included in this review are summarized below, with articles discussing a similar research question grouped together into one of three themes: 1) studies reporting on the influence of remission on physical function in patients using DMARDs, 2) studies reporting on the influence of sustained remission on radiographic progression, and sometimes also physical function in patients using DMARDs & biologicals.
**Chapter 3.2**

<table>
<thead>
<tr>
<th>PubMed: 643</th>
</tr>
</thead>
<tbody>
<tr>
<td>Embase.com: 727</td>
</tr>
<tr>
<td>Cochrane library : 187</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>419 duplicate records removed</th>
</tr>
</thead>
<tbody>
<tr>
<td>1138 records screened (title/abstract) LvT</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>1007 excluded (off topic)</th>
</tr>
</thead>
<tbody>
<tr>
<td>131 records screened (title/abstract) by two independent reviewers (LvT and MB)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>80 excluded (off topic, clearly wrong relation)</th>
</tr>
</thead>
<tbody>
<tr>
<td>52 potentially relevant studies screened (full article)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>41 excluded</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reasons:</td>
</tr>
<tr>
<td>- Similar research question, but not (all) correct variables are studied (n=15)</td>
</tr>
<tr>
<td>- All variables are measured, but no relationship is studied (n=7)</td>
</tr>
<tr>
<td>- Review (n=5) or editorial (n=1)</td>
</tr>
<tr>
<td>- Cross-sectional relationship (n=5)</td>
</tr>
<tr>
<td>- No long term outcomes (n=4)</td>
</tr>
<tr>
<td>- Prediction of remission (n=4)</td>
</tr>
<tr>
<td>- not enough information (n=1)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>11 studies included</th>
</tr>
</thead>
</table>

| 14 potentially relevant studies identified through reference checking/citation tracking |

<table>
<thead>
<tr>
<th>12 excluded</th>
</tr>
</thead>
<tbody>
<tr>
<td>9 potentially relevant studies identified by the expert panel</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>8 excluded</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>3 studies included</th>
</tr>
</thead>
</table>

**Total 14 studies included**

![Figure 1](image)

Flow chart of literature selection

All studies showed that patients who achieve a state of remission, defined in various ways, show less deterioration of function and radiographic progression compared to patients who do not reach a state of remission.

The following two studies reported on the influence of remission on physical function in patients using DMARDs:

**Laborie et al (2002)** performed a cross-sectional questionnaire study to assess very long-term clinical and functional outcomes in RA patients. Of 88 patients, 26 reported a current subjective remission, with a mean duration of 8.5±5.9 months. Of these patients, 20% met the ACR remission criteria. Mean HAQ score for all patients was 1.11±0.84. The median HAQ
score was somewhat lower in the subgroup reporting remission, although considerable overlap occurred with the other patients.

Lindqvist et al (2002)\textsuperscript{12} studied the 10-year outcome in a prospective cohort of early RA patients. They showed that 133 patients (79\%) had relapsing remitting disease (no active joints on examination at least at 1 follow up visit during 10 years). These patients had a significantly lower HAQ (p=0.013) after 10 years than patients with continuous active disease (data not shown). At the 10 year follow up visit 30\%(18\%) patients were in remission for median 13 months.

The following studies reported on the influence of sustained remission on radiographic progression, and sometimes also physical function in patients using DMARDs:

Molenaar et al (2004)\textsuperscript{13} studied the radiographic progression of RA patients that were in clinical remission for at least the preceding 6 months. Clinical remission was defined as a normal erythrocyte sedimentation rate (ESR) and meeting 3 out of 4 remaining ACR remission criteria (fatigue not measured). In the study period the ACR remission definition (meeting 5 out of 5 ACR remission criteria) and the (original) DAS definition (DAS<1.6) was applied. Radiographs of hands and feet were obtained at baseline, 1 and 2 years and were scored according to the Sharp/van der Heijde (SvH)\textsuperscript{14,15} method. Of the 187 included patients, remission persisted in 52\% of the total cohort, 59\% of the patients in ACR remission and 42\% in DAS remission. Compared to patients with an exacerbation during follow up, patients in persistent clinical remission were less likely to have relevant radiographic progression ($\Delta$ SvH$\geq$5) with 23\% vs 7\% respectively (p=0.001). For the ACR criteria these percentages were 10\% vs 7 (p=0.053) and for the DAS definition 17\% vs 6 (p=0.017). Of the patients in persistent clinical remission (as defined by authors) for 2 years, 15\% developed erosions in a previously unaffected joint. The authors concluded that radiological progression can occur during all three defined states of persistent clinical remission.

Aletaha et al (2005)\textsuperscript{16} studied among other things the construct validity of the SDAI and DAS28 by evaluating the association between the time spent in SDAI and DAS28 remission and radiographic progression over 36 months in a cohort of 56 patients with RA. In this study, remission was defined as SDAIs$\leq$3.3 or DAS28$<2.4$. These cut-off values were calculated based on the expert opinion of 35 rheumatologists who judged the disease activity of paper patients (32 different patient profiles). Three groups were compared: patients never in remission, patients 3-18 months in remission, and patients 21-36 months in remission. They found that the longer the patient remained in SDAI remission or DAS28 remission, the less likely the patients were to progress radiologically (p<0.01). A similar relationship was observed with patients in high disease activity: the longer patients remained in high disease activity, the more likely they were to progress radiologically.

Cohen et al (2007)\textsuperscript{17} studied the radiographic progression over 5 years of early RA patients that reached sustained remission (DAS$<1.6$ at the 3-year and 5-year evaluations). Radiographs and HAQs were obtained at baseline, 3 and 5 years. A total of 191 patients were included of whom 36\% achieved remission at 3 years, 28\% at 5 years, and 22\% (n=30) patients were in sustained remission at both 3 and 5 years. This last group was compared with the 104 patients who did not achieve remission at either 3 or 5 years. The total Sharp/van der Heijde score (with interquartile range) at baseline in the remission and non-remission groups was 0.5 (0-7) and 2 (0-7) respectively. At 5 years they were 2.5 (0-14) and 13 (3-29). The progression of damage at 5 years was significantly higher in the group with persistent
disease activity ($\Delta$ total $\text{SvH}=7$ (1-19)) compared to the sustained remission group ($\Delta$ total $\text{SvH}=1.5$ (0-5)) ($p=0.0014$). Still, 10 (33%) patients in sustained remission had a significant increase in radiographic damage between baseline and 5 years. This proportion was 57 (55%) for patients not in remission. Furthermore, 5 (17%) patients in sustained remission had significant radiographic progression between the 3rd and 5th year, and 6 patients developed erosions between the 3rd and 5th year in a previously unaffected joint. Mean HAQ scores were already better at baseline in the remission group: 1.1 (0.7) for the remission group vs 1.4 (0.7) for the non-remission group. At 3 and 5 years the mean HAQ score was 0.2 (0.4) and 0.1 (0.3) for the remission group vs 0.7 (0.6) at both times for the non-remission group. A total of 28 (93%) patients in sustained remission had a HAQ score $\leq 0.5$ at 5 years vs 39 (38%) patients with persistent disease activity ($p<0.001$). The authors concluded that sustained clinical remission according to the DAS criteria <1.6 was associated with stability of radiological damage in most patients and a clear improvement of functional capacity over 5 years in a cohort of patients with early rheumatoid arthritis.

Brown and colleagues (2008) evaluated the long-term significance of subclinical synovitis measured by imaging techniques in patients with clinical remission on conventional DMARD therapy, in relationship to structural outcome. A group of 90 RA patients in remission at baseline were followed for 12 months and radiographs, magnetic resonance imaging (MRI) and ultrasonography (US) were available at both time points. Remission was defined by physician’s clinical judgment and had to be stable for at least 6 months; 54% fulfilled the ACR remission criteria and 56% fulfilled the DAS28 (<2.6) remission criteria. A control group of 17 healthy subjects underwent the same imaging procedures. At 12 months, 17 of 90 (19%) patients experienced a significant deterioration in their total radiographic joint damage scores that was larger than the smallest detectible change. Likewise, 11% of the patients in ACR remission and 12% in DAS28 remission also showed radiographic progression (data not shown). In a binary logistic regression analysis, the authors found that ACR remission protected for adverse structural outcome radiographically (OR=0.33, $p=0.054$). Furthermore, of 25 patients without painful, tender or swollen joints, 4 experienced radiographic progression. The authors concluded that structural progression occurs in RA patients treated with conventional DMARD therapy despite the presence of clinical remission.

Hafström et al (2008) studied if remission (DAS28<2.6) induced by low-dose glucocorticoid treatment in the first two years of the BARFOT study had a sustained effect on radiological damage after 4 years. At 2 years, 55% (n=35) in the prednisolone group and 30% (n=26) in the no-prednisolone group were in remission. At 4 years, 40% of all 150 patients were in remission. Patients in remission at 2 years had significantly less radiographic damage and less change in radiological scores after 4 years compared to those not in remission. Longitudinal analysis showed that DAS28-remission at 2 years was significantly associated with lower Sharp scores during the entire course of observation. The HAQ score at both 2 and 4 years was significantly lower for the patients in remission at 2 years, irrespective of intervention group.

Mäkinen et al (2007) reported the effect of sustained remission on radiographic outcome over 2 years in the FIN-RACo trial. Remission was defined by a modified ACR definition of remission excluding fatigue and by the DAS28<2.6. Sustained remission was defined as remission at 6, 12 and 24 months; radiographs were obtained at baseline, 6 and 24 months. At 6 months, 31 patients were in mACR remission and 72 patients were in DAS28 remission. At 6, 12 and 24 months, 14 patients were in sustained mACR remission, compared to 54 patients who were in sustained DAS28 remission. The authors compared the radiographic
Predictive Validity of Remission progression of the patients in sustained remission, of the patients in remission at 6 but not at 12 or 24 months and of patients not in remission at 6 months. They found a median increase in Larsen score of 0 (95% CI 0-2) in patients in sustained ACR remission, 4 (95% CI 0-10) for patients in ACR remission at 6 months but losing it later and 4 (95% CI 2-8) for patients not in remission at 6 months. For the DAS28 definition of remission, these numbers were 1 (95% CI 0-2), 4 (95% CI 2-16) and 6 (95% CI 2-10). The authors concluded that sustained remission protects against radiographic joint damage.

The following studies reported on the influence of sustained remission on radiographic progression in patients using DMARDs and biologicals:

**Machold et al (2007)** performed a study to determine the frequency of erosive disease and the pace of radiological progression in an inception cohort of patients with very early RA, treated at the discretion of the treating physician. In a subgroup of 55 patients who completed 3 years follow up, 64% developed erosive disease. Longstanding DAS28 remission was seen in 16 patients and was associated significantly with the absence of erosive disease (5 (31%) of these had erosive disease, 2 already at baseline and 3 developed erosions during the 1st year and did not progress any further). Time in remission/low disease activity (DAS28<3.2) correlated negatively with progression in Larsen score. In a stepwise regression model, time in remission/low disease activity showed a significant contribution to overall outcome of damage progression, although the factors with the greatest influence were RF, anti-CCP, CRP and cumulative swollen joint count. Disease modifying anti rheumatic drugs (DMARDs) were used in all patients except two; four patients (all in the erosive group) received tumour necrosis factor (TNF)-α antagonists. The authors concluded that joint damage occurs despite very early treatment.

**Landewé et al (2006)** and **van der Heijde et al (2007)** described the radiographic progression in patients included in the TEMPO trial receiving either MTX monotherapy, etanercept monotherapy or a combination of both. Landewé and colleagues studied the relationship between disease activity and 2-year radiographic progression in this dataset, and found that patients in remission (defined as a time averaged DAS below 1.4 during 1 year) showed less radiological progression than patients with a time averaged DAS above 3.7. They demonstrated that the relationship most often seen (remission or low disease activity leads to less radiographic progression) was not present in the subgroup of patients that was treated with a combination of MTX and etanercept. They suggest that inflammation is not the only cause of radiographic progression and thus that remission or low disease activity does not necessarily lead to less radiographic damage. Van der Heijde and colleagues studied the radiographic progression in patients reaching DAS (<1.6) and DAS28 (<2.6) remission. Although 682 patients started the study drug, 350 patients were withdrawn during the 3 years. DAS /DAS28 remission was reached by 145(28%)/152(30%) in year 1, 154(37%)/157(38%) in year 2, and 117(38%)/124(41%) in year 3 (completers only). In patients who achieved DAS remission, radiographic remission (change in total sharp score ≤0.5) was also attained in 85%, 80%, and 56% of patients in the combination, etanercept, and methotrexate groups, respectively. Conversely, fewer patients in the group not achieving DAS remission showed stability of radiographic progression (change in total sharp score >0.5) (34%, 45%, and 58% of patients in the respective treatment groups).

**In 2006, Smolen et al** also reported on data of the ASPIRE trial, with disease activity divided into tertiles with the lowest tertile a DAS<2.85. In the group that was treated with MTX monotherapy, patients with a higher DAS score at 14 weeks had more radiological
<table>
<thead>
<tr>
<th>Study (ref)</th>
<th>n</th>
<th>Disease duration (mean, y)</th>
<th>Study type</th>
<th>Intervention</th>
<th>Remission definition</th>
<th>% patients in remission</th>
<th>Remission duration</th>
<th>Follow up (y)</th>
<th>Remission beneficial for outcome measure:</th>
<th>Contrast</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laborie 2002</td>
<td>88</td>
<td>20</td>
<td>Retrospective cohort</td>
<td>Rheumatologists’ choice, DMARDs and glucocorticoids</td>
<td>- Patient reported - Patient reported ACR criteria</td>
<td>29</td>
<td>Mean 8.5 mo</td>
<td>-</td>
<td>Median HAQ score</td>
<td>Patients in vs not in remission</td>
</tr>
<tr>
<td>Lindqvist 2002</td>
<td>168</td>
<td>0.9</td>
<td>Cohort</td>
<td>Rheumatologists’ choice, DMARDs and glucocorticoids</td>
<td>mACR</td>
<td>79</td>
<td>Minimum 1 time point</td>
<td>10</td>
<td>Mean HAQ scores for patients after 10 y</td>
<td>Patients in relapsing remittive disease vs continuously active disease</td>
</tr>
<tr>
<td>Molenaar 2004</td>
<td>187</td>
<td>Median 7</td>
<td>Cohort</td>
<td>Rheumatologists’ choice: DMARDs</td>
<td>- mACR + ESR - mACR - DAS&lt;1.6</td>
<td>100 with 52 sustained 59 with 59 sustained 81 with 42 sustained</td>
<td>2.5 y</td>
<td>2</td>
<td>% of patients with Δ SvH ≥5</td>
<td>-</td>
</tr>
<tr>
<td>Aletaha 2005</td>
<td>56</td>
<td>?</td>
<td>Inception cohort</td>
<td>Unknown</td>
<td>SDAI&lt;3.3 DAS28&lt;2.4</td>
<td>?</td>
<td>Never vs 3-18 mo 21-36 mo</td>
<td>3</td>
<td>Change in Larson score between baseline and 3 y</td>
<td>-</td>
</tr>
<tr>
<td>Cohen 2007</td>
<td>134</td>
<td>0.7</td>
<td>Cohort</td>
<td>DMARDs</td>
<td>DAS&lt;1.6</td>
<td>22 at 3 and 5 yrs</td>
<td>2 y</td>
<td>5</td>
<td>Change in SvH score at baseline, 3 and 5 y</td>
<td>Continuous and dichotomous HAQ scores</td>
</tr>
<tr>
<td>Brown 2008</td>
<td>90</td>
<td>Median 7</td>
<td>Cohort</td>
<td>DMARDs</td>
<td>- Rheumatologists’ judgement - ACR criteria - DAS28&lt;2.6</td>
<td>100</td>
<td>Median 2 y before inclusion</td>
<td>1</td>
<td>Change in Genant modified Sharp score over 1 y</td>
<td>-</td>
</tr>
<tr>
<td>Häfstrom 2008</td>
<td>150</td>
<td>0.5</td>
<td>RCT extension</td>
<td>1: DMARDs 2: DMARDs + pred</td>
<td>DAS28&lt;2.6</td>
<td>55 at 2 y 40 at 4 y</td>
<td>Minimum 1 time point</td>
<td>4</td>
<td>Change in SvH and absolute scores at 0, 2 and 4 y</td>
<td>HAQ score at 2 and 4 y</td>
</tr>
<tr>
<td>Study</td>
<td>Year</td>
<td>N</td>
<td>Included Treatments</td>
<td>Outcomes</td>
<td>Duration</td>
<td>Data Points</td>
<td>Follow-up</td>
<td>Patients Description</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------------------------------</td>
<td>------</td>
<td>----</td>
<td>--------------------------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------</td>
<td>----------</td>
<td>-------------</td>
<td>-----------</td>
<td>--------------------------------------------------------------------------------------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mäkinen 2007 (169)</td>
<td>2007</td>
<td>169</td>
<td>1: SSZ 2: SZZ + MTX + HCQ + pred                                                    - mACR - DAS28&lt;2.6</td>
<td>8 sustained vs 92 not sustained 32 sustained vs 68 not sustained</td>
<td>1.5 y</td>
<td>2</td>
<td>Change in Larson score between 0, 6, 12 and 24 mo                                                    - Patients not in remission, in remission and in sustained remission.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Machold 2007 (55)</td>
<td>2007</td>
<td>55</td>
<td>Cohort Rheumatologists’ choice. DMARDs + glucocorticoids + 4 patients anti-TNF       - DAS28&lt;2.6 for at least 1 y - DAS28&lt;3.2</td>
<td>29</td>
<td>1 y</td>
<td>3</td>
<td>Development of erosions yes/no, score, Larson-Scott                                                  - Patients in 4 different categories of disease activity.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Landewé 2006 (444)</td>
<td>2006</td>
<td>444</td>
<td>1: MTX 2: Etanercept 3: MTX+etanercept                                               Time averaged DAS (12 mo&lt;1.6)</td>
<td>9</td>
<td>Mean 1 y</td>
<td>1</td>
<td>Annual change in SvH score, calculated from 0, 1 and 2 y data                                       - Patients in 4 different disease activity categories.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Van der Heijde, 2008 (332)</td>
<td>2008</td>
<td>332</td>
<td>1: MTX 2: Etanercept 3: MTX+ etanercept                                             - DAS&lt;1.6 - DAS28&lt;2.6</td>
<td>28 at 1 yr 37 at 2 yr 38 at 3 yr 30 at 1 yr 38 at 2 yr 41 at 3 yr</td>
<td>3</td>
<td>Minimum 1 time point</td>
<td>Change in SvH score                                                  - Patients reaching DAS remission vs not reaching this state</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smolen 2006 (1004)</td>
<td>2006</td>
<td>1004</td>
<td>1: MTX 2: MTX + IFX 3mg/kg 3: MTX + IFX 6mg/kg                                     DAS28&lt;2.84</td>
<td>30 at wk 14</td>
<td>Minimum 1 time point</td>
<td>1</td>
<td>Change in SvH between 0 and 54 wks                                                                   - Patients in different disease activity states categorized by DAS28 tertiles.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smolen 2008 (1049)</td>
<td>2008</td>
<td>1049</td>
<td>1: MTX 2: MTX + IFX 3mg/kg 3: MTX + IFX 6mg/kg                                    - SDAIs≤3.3 - CDAIs≤2.8 - DAS28&lt;2.6</td>
<td>19 at wk 14 15 at wk 54 20 at wk 14 22 at wk 14</td>
<td>Minimum 1 time point</td>
<td>1</td>
<td>Change in SvH between 0 and 54 wks                                                                   - Patients reaching remission at 14 wks, at 54 wks, or no remission.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aletaha 2009 (510)</td>
<td>2009</td>
<td>510</td>
<td>1: MTX 2: Adalimumab 3: MTX + adalimumab                                           SDAIs≤3.3</td>
<td>23</td>
<td>1 y</td>
<td>2</td>
<td>Change in total Sharp score during the second y of study while in remission                         - For patients with another 3, 6 or 9 months in remission</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

mACR: modified ACR criteria, often excluding fatigue
progression between baseline and week 54 than those with lower DAS scores (p<0.05). There was little progression in the MTX+IFX group, even in patients in the highest DAS28 tertile. Analyses using SDAI tertiles to define disease activity produced similar results. The authors concluded that higher disease activity was associated with greater radiographic damage in the MTX group, while little progression occurred in the combination group.

Smolen et al (2008) reported on data from the ASPIRE trial, studying the effectiveness of methotrexate (MTX) alone compared to MTX plus infliximab (IFX). Disease activity was classified into 4 states with the SDAI≤3.3 as remission. Of the 1049 patients who started the study, 155 (15%) patients reached SDAI remission at 54 weeks and the radiographic progression of these patients was lower than that of the patients in the other disease activity states. In general, patients treated with MTX plus IFX showed less radiographic progression across all disease activity states, while in patients using MTX monotherapy, joint damage increased with every disease activity category. 78 (7%) achieved SDAI remission at 14 weeks and these patients had very limited radiographic progression at week 54, even on MTX. This study showed that sustained remission even on MTX (if seen already at week 14) is associated with no radiographic progression on the group level.

In 2009, Aletaha and colleagues studied the rate of radiological progression in patients in sustained remission in a post-hoc analysis of the PREMIER trial (comparing effectiveness of either methotrexate monotherapy, adalimumab monotherapy or a combination of both). They studied the radiographic damage in a subgroup of patients that was in sustained remission defined by SDAI≤3.3 during months 12 and 24 of the PREMIER study, and compared the groups with an additional preceding remission period of either 3, 6 or 9 months. They found that the shorter the period of remission, the more likely some mild progression may be found, which was deemed a consequence of a carry-over effect of past periods of inflammation. The authors concluded that preceding disease activity is a relevant determinant for radiographic progression between two time points.

DISCUSSION
This systematic review identified only 14 studies reporting on the longitudinal relationship between a definition of remission and long term outcome of RA in terms of function and/or radiographic progression. Fortunately, all studies showed that patients that achieve a state of remission, defined in various ways, show less deterioration of function and radiographic progression compared to patients that do not reach a state of remission. It is remarkable that there are only 14 studies that report on this subject, while this data is probably available in many follow up studies of clinical trials. Many studies had to be excluded because they reported on the relationship between remission and long term outcome at the same time point, studied the relationship between disease activity and long term outcome without defining remission, or collected all the relevant variables but did not look at the relationship between them. Although no limitations for year of publication were used, the oldest articles included in this review are from 2002, by Lindquist et al and Laborie et al. It was expected to find older articles, since the first official remission definition was proposed by Pinals et al in 1981. On the other hand, remission did not occur often before the introduction of combination DMARD therapies and anti-TNF strategies in the last decade.
While all of the reviewed articles examined remission and stability of longer term outcomes, the temporal relation of remission to those longer term outcomes varied a bit from study to study. Most of the reviewed studies assessed remission during the period when longer term stability was also being assessed. Since change in longer term outcomes was occurring at the time remission was assessed, these studies might not be considered longitudinal. We are not
Predictive Validity of Remission

sure if any evaluated remission preceding the period in which long term outcomes were assessed (e.g. remission at 6 months; long term outcomes from 6 months to 2 years). Therefore the predictiveness of remission for later radiographic or functional stability is unclear.

Because the topic of this review is often not the primary goal of a study, our search strategy had to be sensitive enough to find the eligible articles, even when the topic was not mentioned in the abstract. Although we used a sensitive search strategy, it is possible that relevant articles were missed, because these findings were reported in a sub analysis. Nevertheless, we believe we are rather complete in our search, especially by including a round with the experts that are currently designing a new definition for remission in RA, who could identify only one additional relevant study. The consistency of the results of the included articles makes it very likely that this is the true direction of the signal with those patients achieving a state of remission showing less deterioration of radiographic progression and function.

It is important to report on this specific research question because increasing numbers of trials use remission as an important outcome, assuming that this leads to favourable long term outcomes. The current review confirms that there is evidence for a longitudinal relationship between remission and long term RA outcome, but more research is needed to confirm this finding.

Another interesting development in the relationship between remission and radiographic progression is the so called ‘disconnect’ between disease activity and radiological damage as hypothesized by Kirwan et al\textsuperscript{22,24,25,28,29}. According to this hypothesis, disease activity (or inflammation) only partly explains long-term radiological damage. The articles by Landewé et al\textsuperscript{22} and Smolen et al\textsuperscript{25} included in this review strongly suggest that most patients treated with biologic therapies experience a virtual halt of radiographic progression, regardless of disease activity, whereas in patients treated with monotherapy there was increasing joint damage with increasing disease activity. However, even on biologics a slight progression of joint damage can be observed with increasing disease activity. Moreover, methods for identifying progression are insensitive in the setting of very low progression rates, as the smallest detectible difference is about 5 Sharp/van der Heijde points, while the progression is close to 0\textsuperscript{30}. Furthermore, clinical methods are unreliable in the setting of very low disease activity.

The study by Brown et al\textsuperscript{18} included in this review shows that radiographic progression in patients in clinical remission is mostly explained by subclinical joint inflammation detected by ultrasound and MRI. It thus remains possible that the reduction in association is in fact explained by subclinical synovitis occurring less frequently in patients in remission induced by biologic or combination therapies than in patients in remission induced by monotherapy. On the other hand, the study by Aletaha et al\textsuperscript{26} and Smolen et al\textsuperscript{25} suggests that it is primarily the sustained remission which will allow joint damage to halt, indicating that either a carry-over effect occurs or subclinical disease activity may still be present driving joint damage, before it is ultimately arrested. One way or the other, the validation of a remission definition based on clinical measurement must take account of the reduced association between disease activity and structural damage demonstrated by these studies.

Although all remission definitions lead to reduced radiological progression, some definitions still allow significant residual disease activity while others are more strict, allowing no swollen or tender joints\textsuperscript{11}. It has been shown that the exclusion of the ankles and feet in reduced joint counts can give different results and should be used with caution in clinical practice\textsuperscript{31,32}. This might explain at least a proportion of the joint damage that occurs in such states of remission. As can be learned from this review, the current concept of remission is complex and the development of a new definition a big challenge. This review, albeit of a very limited number of studies, offers consistent evidence that remission by all currently applied definitions is longitudinally related to radiological progression and physical function.
REFERENCES


32. **Landewe R**, van der Heijde D, Van Der Linden S, Boers M. Twenty-eight-joint counts invalidate the DAS28 remission definition owing to the omission of the lower extremity joints: a comparison with the original DAS remission. *Ann Rheum Dis* 2006;65(5):637-41.
SUMMARY &
GENERAL DISCUSSION
This thesis comprises qualitative and quantitative research around three important topics in the field of modern rheumatoid arthritis treatment: 1) combination therapy, a treatment strategy in which different drugs are combined to give better response and improved outcome compared to single DMARD therapy (monotherapy); 2) monitoring strategies, regular measurements (monitoring) of disease activity and subsequent adjustment of therapy to achieve better disease control; and 3) remission, the so called ‘absence of disease’.

Section I presents research around implementation of the original COBRA combination therapy; section II introduces an intensified combination therapy, combined with a new monitoring strategy. The concept of combination therapies as well as monitoring strategies is based on the knowledge that early intervention with a powerful therapy can prevent long term damage and improve outcome. The third topic of this thesis, remission, is also related to improved outcome, as this is the ultimate goal of treatment in rheumatoid arthritis. Section III of this thesis shows that achieving remission leads to improved outcome, but that the concept of remission is not as straightforward as ‘the absence of disease’.

SECTION I: IMPLEMENTATION OF COBRA THERAPY
Chapters 1.1 to 1.5 constitute the body of this thesis, all revolving around the legacy of the COBRA trial\textsuperscript{1,2}. The results of this trial that contributed to a changing view on treatment of patients with RA, were not automatically picked up by practitioners, nor implemented in clinical practice. The reasons for this were investigated in two phases.

Attitudes and opinions of rheumatologists and patients towards COBRA therapy (Chapters 1.1 & 1.2)
In the first phase, the attitude of physicians towards COBRA therapy was measured through a small questionnaire, sent to every rheumatologist in The Netherlands. From the responses we learned that COBRA therapy was regarded as effective and safe, but also complicated to administer. Remarkably, the overall attitude of rheumatologists towards COBRA therapy was positive, the majority of responding rheumatologists did not intend to prescribe COBRA therapy in the near future. These results gave us a first indication of the contradictory feelings around the use of COBRA therapy\textsuperscript{3}.

In the second phase, we organised focus group discussions with both patients and rheumatologists (in separate groups). For rheumatologists, these focus group discussions confirmed the results found in the first phase of this study, but provided more in-depth information that was necessary to understand the discrepancies between attitude and intention. Rheumatologists were positive about the effectiveness of COBRA therapy, but highly concerned about their patients’ possible negative reaction to the large amount of pills to be prescribed. Doctors feared to fail in the eyes of their patients in prescribing such a disagreeable therapy. In addition, rheumatologists perceived lack of time explaining and prescribing COBRA therapy and felt uncomfortable prescribing high doses of prednisolone\textsuperscript{4}.

On the other hand, patients were positive about an aggressive combination therapy such as COBRA therapy, and they had no qualms taking many pills if this would give immediate relief or might improve their prognosis. Patients associated prednisolone with negative side effects (especially affecting looks), but they were also aware of its benefits and the need of prednisolone in rough times. Patients stated they based their opinions on their own experience at the start of the disease and concluded that taking a lot of pills is better than the pain and constraints they faced with the disease. A decrease in the amount of pills after a period of intensive treatment was highly appreciated. A limitation of this research was the disease duration of the patients; most patients had more than 10 years of experience with the disease and were diagnosed in a time when not many treatments were available. They
experienced a lot of pain, limitation of function and damage of joints. Currently, patients with inflammation or swelling in only a few joints can be recognised as RA (or soon to be RA) and are directly treated effectively. Nevertheless, results of the focus groups with patients showed that if the disease is aggressive, patients are more than willing to undergo a temporary period of taking many pills and even prednisolone if this improves their function and prognosis. An important issue for rheumatologists was the lack of scientific comparison between COBRA therapy and their current first choice of treatment (mostly methotrexate (MTX) with sometimes low-dose bridging prednisolone). Independent of this thesis, a trial has been designed and started in Amsterdam (the so called COBRA-light trial) to investigate the difference between the original COBRA therapy and a light-version with a lower dose of prednisolone, a higher dose of MTX and no sulfasalazine (SSZ).

11-year follow up of the COBRA cohort (Chapters 1.3 & 1.4)

Rheumatologists also indicated they were worried about the long term effects of the initial high dose prednisolone. In response, we performed a long-term follow up study of the COBRA trial. This study revealed that there were no real differences in long term outcome between the two treatment groups that could be contributed to the initial study drugs. Mortality in the COBRA group was numerically lower, and cardiovascular and other major comorbidities similar to that in the SSZ group. The prevalence of hypertension and diabetes were increased, but offset by a decrease in hypercholesterolemia. Prevalence of osteoporosis was also highly comparable. Moreover, after 10 years of therapy at the discretion of the treating physician, benefits on the disease itself, as previously demonstrated in damage progression after 5 years are maintained and perhaps even continue to increase after COBRA therapy, depending on how one deals with the selective drop-out. Unfortunately, every long-term follow up study is faced with patients that are lost to follow up. In our study, more patients with a poor prognosis in the SSZ group were lost to follow up compared with the loss to follow up in the COBRA group. Linear imputation of missing data according to every patient's individual progression rate was the closest we could come to a best estimate of a difference in progression rates between the groups. Caution has to be taken when imputing missing data; bias can easily be introduced. Using ‘a last observation carried forward’ approach for example would assume no progression of radiographic damage in the patients that were lost to follow up. Linear imputation of data assumes a linear relationship between time and progression, which is also not applicable to every patient. However, the bias introduced by selective drop-out is also unacceptable. For that reason, we chose to present two models; the model with selective drop-out, in which the SSZ group and COBRA group have an equal progression rate, although the Sharp/van der Heijde score at every time point in the COBRA group is over 4 points below the SSZ group; and the model with linear imputation of missing data showing a continued benefit in terms of a significant delay in progression rate between the COBRA group and SSZ group. Most importantly, the research presented in Chapter 1.3 shows COBRA therapy is as safe as other anti-rheumatic therapies.

The data collection of such a long follow up of RA patients gave us the opportunity to investigate predictors of long term RA outcome. Baseline predictors are important, because this gives rheumatologists the opportunity to identify patients with a poor prognosis in an early stage of the disease. Previous research on the COBRA dataset highlighted the predictive ability of bone markers reflecting bone and cartilage degradation resulting from joint destruction in RA: high baseline levels of urinary excretion of C-terminal cross linking of type-I and type-II collagen (CTX-I and CTX-II) independently predict an increased risk of radiological progression over 5 years; moreover, the individual CTX-II response of patients measured
after 3 months of therapy independently predicts long-term radiographic progression. Another marker for bone loss (or more specifically for osteoclast activation) is the ratio between receptor activator of nuclear factor-κB ligand (RANKL) and osteoprotegerin (OPG). Geusens and colleagues showed in the follow up data of the COBRA trial that low baseline OPG:RANKL-ratios of early untreated RA patients could predict radiological progression.

In chapter 1.4, we show that CTX-I, CTX-II and the RANKL:OPG ratio are strong, independent predictors of annual radiological progression over 11 years in data of the COBRA trial. The identification of patients with high baseline levels of CTX-I, CTX-II and especially a high RANKL:OPG ratio can help to estimate the severity of the disease and point to indication for aggressive treatment. It is a shortcoming of our study that anti-CCP was not measured in this cohort since anti-CCP is one of the strongest predictors of radiological damage. The predictive ability of CTX-I, CTX-II and the RANKL:OPG ratio should be further investigated in a multivariate model including anti-CCP. Furthermore, as there is evidence from animal models that the inhibition of RANKL could prevent new erosions to occur, it is important to investigate the effect of different treatment strategies on the RANKL:OPG ratio alongside the longitudinal development of new erosions.

Design and pilot testing of an implementation plan (Chapter 1.5)

After we had evaluated all aspects of COBRA therapy from the patient and rheumatologist point of view, as well as the long term effects on disease progression, we designed an implementation strategy. The central question in this practical part of our research was how to make it easier and more agreeable for rheumatologists, patients but also arthritis nurses to use COBRA therapy in clinical practice. Many clues for improvement of daily use by rheumatologists as well as patients were extracted from the rich data gathered during focus group discussions. Rheumatologists felt COBRA therapy is complicated and takes a lot of time to prescribe. Furthermore, they felt that patients might object to the use of a large amount of pills, including prednisolone. To ease the workload, we made a patient information booklet, including visual aids to explain the therapy, clear tables on the intake of the different drugs and pre-printed prescriptions to speed up the prescribing process. We also disseminated the results of the patient focus groups, in which patients explained that the temporary use of a large amount of pills or prednisolone was acceptable, as long as this would take away their immediate complaints and improve their prognosis. To further improve the patients comfort while using COBRA therapy, the patient information material also contained an interview, in which a fictional early RA patient explained her feelings during diagnosis and start of COBRA therapy. The content of this interview was also derived from the focus group discussions with patients, and was used in the booklet to give patients a positive boost when starting this therapy. We provided a group of motivated rheumatologists and arthritis nurses with this implementation material and asked them to prescribe COBRA therapy to their patients using the supplied material. All parties, rheumatologists, patients and nurses, evaluated the material and gave very positive judgements. The website, containing the patient information material as well as all the scientific research around COBRA therapy presented at congresses, articles and this thesis, is currently online at www.cobratherapy.nl. With this pilot study, the material is ready to be implemented in clinical practices around the world.

To investigate the impact of our COBRA implementation study, digital pharmacies can help to quantify the increase in number of specific prescriptions. We intent to measure the amount of COBRA prescriptions well before start, and well after closure of this study by running a query on the amount of prescriptions of a combination of SSZ, MTX and prednisolone for the
diagnosis of RA. Importantly, we will do this well after the publication of this thesis, to prevent biased results due to a temporary focus on COBRA therapy.

SECTION II: COBRA-CTX STUDY
Parallel to the implementation study described above, the growing literature on effectiveness of monitoring strategies made us wonder about the benefits of a modified COBRA treatment, complemented with a monitoring strategy. Several studies showed the effectiveness of monitoring on disease activity\textsuperscript{13-16}, but other studies show that damage progression may be partially independent of disease activity, leading to the hypothesis that clinical disease activity and radiological damage are mediated by different disease processes\textsuperscript{17}. It has been suggested that uncoupling of damage progression and disease activity occurs in patients without clinical benefit that still show slowing of progression\textsuperscript{18,19}, and conversely in patients in clinical remission that still show progression\textsuperscript{20}. In this setting, monitoring on a more direct marker of radiological progression might be more beneficial.

The COBRA-CTX-II pilot trial (Chapter 2.1 & 2.2)
Joint damage in rheumatoid arthritis is reflected by bone and cartilage degradation. As discussed in chapter 1.4, two markers that have been identified to measure the extent of bone and cartilage degradation are CTX-I and CTX-II\textsuperscript{21}. In data of the COBRA trial, CTX-II was able to predict radiological progression over 5 years follow up better than rheumatoid factor, baseline damage and disease activity\textsuperscript{5,6;22}. Furthermore, a level of CTX-II could be identified below which almost no further radiological progression occurred and which is similar to levels of healthy controls\textsuperscript{23}. This made us hypothesize that CTX-II might be more useful as a monitor for treatment intensification than disease activity measured by the 28 joint count DAS.

To investigate the feasibility to test such a hypothesis in a clinical trial setting, we performed a pilot trial comparing monitoring strategies based on either frequent measurement of DAS28 or of urinary excretion of CTX-II. Patients were randomised to be monitored by either strategy, with an intensification of therapy if the DAS cut point or the CTX-II cut point was not achieved. To make sure that all patients were treated effectively, everyone received an intensified version of the COBRA therapy, added with hydroxychloroquine from baseline and intensified with increasing dosage of MTX if the cut point was not reached at 8 weeks and introduction of infliximab if the cut point was not reached by 21 weeks.

This intensive treatment strategy, in combination with strict monitoring, proved to be feasible and resulted in 90% of patients reaching a state of DAS remission, the highest remission rate reported in the literature up to date\textsuperscript{24}. In contrast, a CTX-II remission was less easily attained, and was independent of more aggressive treatment intensification in the CTX-group.

The high remission rate in our study is best explained by the intensive treatment schedule. Compared to previous trials, more drugs were used at higher doses, and treatment could be intensified as early as 8 weeks into the trial.

We also showed that this intensive conventional DMARD therapy, including initial high dose prednisolone according to the COBRA schedule can rapidly decrease both IgM rheumatoid factor (RF) and anti-CCP serum levels by more than 50% during this pilot trial. Rapid decreases in RF have also been documented in the original COBRA trial and by several others\textsuperscript{29-30} but to our knowledge, such profound decreases of anti-CCP during treatment of early RA patients have not been described before. Since the presence of RF and anti-CCP antibodies in early disease are associated with more severe disease and rapid radiological progression\textsuperscript{31,32}, monitoring anti-CCP levels alongside disease activity might increase the efficacy of treatment strategies aimed at preventing damage and disability.
The effect of CTX-II monitoring on radiological progression could not be evaluated due to the small amount of patients and the large differences in baseline Sharp/van der Heijde scores between the patients. A limitation of this study is its open approach and small sample size. Allocation to monitoring strategy was blinded, but study personnel and patients were aware that treatment consisted of a very effective therapy. This may have exaggerated response, but a 90% remission rate is unlikely to be caused by expectation bias. Despite the preliminary nature of a pilot trial, these results strengthen the suggestion that intensive conventional treatment including initial high oral prednisolone, and infliximab add-on where necessary, can lead to new levels of disease control in early RA.

These results support the organisation of a larger trial, in which the effect of CTX-II monitoring on radiographic progression can be studied, and the effectiveness and safety of the treatment strategy further investigated.

**SECTION III: ACR/EULAR/OMERACT REMISSION INITIATIVE**

A third development described in this thesis is the increasing state of confusion around the best way to define remission in RA. In the COBRA-CTX-II-study mentioned above, 90% of patients reached DAS28 remission, but only 45% reached remission defined by the ACR criteria. Recent studies that measured remission using several different definitions all encounter the same problem: the use of different definitions to measure remission in RA lead to different results in remission rates, invalidating comparisons between trials.

**Defining remission in rheumatoid arthritis (Chapter 3.1 & 3.2)**

The ACR, EULAR and the OMERACT initiative decided to join forces to work towards a new uniform definition of remission with optimal performance in clinical trials and feasibility in clinical practice (although these definitions might not be exactly the same). An international committee of experts in the field of remission was invited to discuss on the research agenda, resulting in the first boundaries for a future definition of remission; experts felt that a strict definition was necessary, unlike the DAS28 that allows for joints in the feet to be swollen or painful. Furthermore, it was felt that the remission definition should be validated against radiographic progression and function: a good definition should be able to differentiate between patients with continued progression or worsening of function and patients with improved outcomes. Because it was unknown to what extent current definitions of remission are able to differentiate between these states, we reviewed the literature on the relationship between remission and long term radiological progression and function. This showed that all patients that reach a state of remission, defined in various ways, have an improved outcome. It also highlighted the complexity described above; patients in clinical remission can still show progression and especially during biologic treatment, patients with continued disease activity can still show a halt of radiological damage, suggesting an alternative pathological process. More research is needed to study this ‘disconnect’ hypothesis and to explain the difference in response to DMARD versus biologic treatment. At this moment, datasets of RA clinical trials from around the world are being analysed to study which variables have the best measurement properties and are suitable candidates to include in a future remission definition.

**THE WAY FORWARDS**

COBRA therapy is effective, safe, and with the proper material easy to use in clinical practice by patients as well as rheumatologists and arthritis nurses. Moreover, national implementation of COBRA therapy as a first choice for newly diagnosed RA patients with an aggressive arthritis is sensible, not only from a medical perspective, but also from an economic and
patient point of view. Since COBRA therapy is a combination of inexpensive, generic drugs, it is a highly cost-effective treatment of early RA. Patients would benefit from implementation of COBRA therapy, because this therapy gives them a better prognosis than DMARD monotherapy. Therefore, it is highly recommended to rheumatologists around the world to advice COBRA therapy to active RA patients on first presentation. In case of failure of response, patients can rapidly switch to a biological in combination with methotrexate, since the conditions set by some national authorities to have failed on at least two DMARDs have been met. This strategy ensures fast, effective as well as cost-effective treatment for early active RA patients, increasing their chances on regaining their quality of life and preventing long term damage to their joints.

When effective therapy is combined with frequent measurements of a marker of disease activity, the treatment of patients that do not respond well can be rapidly adjusted. We have shown that a larger study is feasible and necessary to study the effectiveness and safety of intensified COBRA therapy, and the effectiveness of a monitoring strategy based on bone degradation markers. And instead of focusing solely on CTX-II as a marker of cartilage degradation, we have shown that combined measurements of RANKL:OPG and CTX-II might be even more important when aiming for long term damage arrest. Research is needed to investigate the response of RANKL:OPG to effective treatment. If this marker behaves similar to CTX-II, a future monitoring trial could clarify their sole or combined role as indicators of improved long term outcome in RA patients. The response of RANKL:OPG to treatment in our pilot study is therefore one of the first on our research agenda. In the meantime, research has shown the benefit of monitoring on the DAS; implementation of this monitoring strategy is very important and should soon be a standard in all hospitals that care for RA patients.

Development of a new remission definition is a big challenge, giving the uncertainties around the pathological pathway of bone destruction and the optimal way to measure inflammation. Despite these uncertainties, research shows that all currently available remission definitions lead to a more favourable outcome on the long term. I would therefore recommend to continue to aim for remission in a way that is feasible at the local care-giving facilities, while closely monitoring the progress of the expert committee on the definition of remission. The combined expertise of both ACR, EULAR and OMERACT provide the ultimate environment to create and implement a new measure of remission for both trials and clinical practice.
KEY FINDINGS
- COBRA therapy is not very popular with rheumatologists because they feel it is a complicated and time consuming therapy to prescribe and believed to be feared by patients.
- Patients have no objections to an initial aggressive therapy including initial prednisolone or many pills, as long as it is temporary and improves their prognosis.
- COBRA therapy is as safe as other anti-rheumatic therapies on the long term and might even benefit patients 11 years after treatment initiation.
- Providing rheumatologists and patients with tailored information material facilitates the use of COBRA therapy in clinical practice.
- Markers of bone and cartilage degradation measured before start of treatment are strong predictors of future radiological damage.
- To prevent future radiological damage, a trial with intensified COBRA therapy and monitoring strategy based on bone marker (CTX-II) measurements is feasible; moreover, such a trial is warranted, given the uniquely high remission rates and sharp decreases of rheumatoid factor and anti-CCP observed in our pilot study.
- Currently available remission definitions in RA generally predict favourable long term outcome, but the definition of remission in RA is unsatisfactory. An international committee of experts in the field of remission is charged with the task to redefine remission in RA.
REFERENCES


SAMENVATTING & DISCUSSIE
CURRICULUM VITAE
PUBLICATIES
&DANKWOORD

(Dutch summary & discussion, curriculum vitae, publications & acknowledgment)
Samenvatting & Discussie

Dit proefschrift bestaat uit kwalitatief en kwantitatief onderzoek gericht op drie belangrijke onderwerpen binnen de moderne behandeling van reumatoïde artritis (RA):

1) combinatie therapie, een behandelmethode waarbij verschillende geneesmiddelen gecombineerd worden voor een optimale respons en een verbetering van de ziekte in vergelijking met monotherapie; 2) monitoring strategieën, het gestructureerd meten (monitoren) van ziekteactiviteit en het hierop aanpassen van de medicamenteuze behandeling om zo de ziekte beter te controleren; en 3) remissie, of 'de afwezigheid van ziekte', het ultieme doel van de behandeling.

sectie I van dit proefschrift presenteert de implementatie van de originele COBRA combinatie therapie en sectie II introduceert een geïntensiveerde combinatietherapie, in combinatie met een nieuwe monitoringsstrategie. Zowel combinatietherapiën als monitoringsstrategieën zijn gebaseerd op wetenschappelijke bewijzen dat vroege interventie met een krachtige therapie schade op de lange termijn kan voorkomen en een betere ziekte-uitkomst geeft. Het derde onderwerp in dit proefschrift, remissie, is ook gerelateerd aan verbeterde ziekte-uitkomst. Sectie III van dit proefschrift laat zien dat het behalen van remissie leidt tot verbeterde ziekte-uitkomst op de lange termijn, maar dat het concept 'remissie' niet zo simpel is als 'afwezigheid van ziekte'.

sectie I: Implementatie van COBRA Therapie

De hoofdstukken 1.1 t/m 1.5 beschrijven het onderzoek rondom de implementatie van COBRA therapie en zijn gebaseerd op de uitkomsten van de originele COBRA trial\(^1\).\(^2\). De resultaten van deze trial hebben in belangrijke mate bijgedragen aan de verandering van de kijk op het behandelen van patiënten met RA. Desondanks werden de resultaten niet automatisch overgenomen door clinici of geïmplementeerd in de dagelijkse praktijk. De redenen hiervoor werden onderzocht in twee verschillende fasen.

Attitudes en meningen van reumatologen en patiënten ten aanzien van de COBRA Therapie (Hoofdstukken 1.1 & 1.2)

In de eerste fase van deze studie werd de attitude van reumatologen ten aanzien van COBRA therapie gemeten met behulp van een korte vragenlijst die naar iedere reumatoloog in Nederland werd gestuurd. Uit de reacties bleek dat COBRA therapie als effectief en veilig werd ervaren, maar ook als ingewikkeld. Opvallend was dat de gemiddelde attitude ten aanzien van de COBRA therapie positief was, terwijl de grote meerderheid van de reumatologen niet van plan bleek om COBRA therapie in de nabije toekomst voor te schrijven aan een patiënt. Deze resultaten gaven ons een eerste indicatie van de tegengestelde gevoelens rondom het gebruik van de COBRA therapie\(^3\).

In de tweede fase van deze studie hebben we focus groep discussies georganiseerd met zowel reumatologen als patiënten (in aparte groepen). In de focus groep discussies met reumatologen werden de resultaten van de eerste fase van deze studie bevestigd. Deze resultaten gaven ook een achtergrond die nodig was om de tegenstrijdigheid tussen态度 en intentie te begrijpen. Reumatologen waren positief over de werkzaamheid van COBRA therapie, maar maakten zich grote zorgen over de mogelijk negatieve reactie van de patiënt bij het voorschrijven van een grote hoeveelheid pillen. Artsen waren bang te falen ten opzichte van hun patiënt als ze een in hun ogen vervelende therapie zouden voorschrijven. Daarnaast gaven reumatologen aan over te weinig tijd te beschikken om COBRA therapie voor te schrijven en uit te leggen en voelden zij zich ongemakkelijk bij het voorschrijven van een hoge dosis prednisolon\(^4\). In tegenstelling tot de reumatologen waren de patiënten erg positief over het gebruik van een krachtige combinatie therapie als COBRA en hadden ze er geen problemen mee om tijdelijk
veel pillen in te nemen als dit verlichting van de klachten zou geven en hun prognose zou kunnen verbeteren. Patiënten associeerden prednisolonen met vervelende bijwerkingen (met name met betrekking tot het uiterlijk), maar waren zich ook bewust van de noodzaak van prednisolonen in moeilijke tijden. Zij baseerden hun mening op hun eigen ervaringen in de beginfase van de ziekte en concludeerden dat het tijdelijk innemen van veel pillen aanzienlijk beter is dan de pijn en beperkingen die zij ervoeren met de ziekte. Wel werd de afname van de hoeveelheid pillen na een periode van intensieve behandelen zeer op prijs gesteld. Een beperking van dit onderzoek lag in de ziekteperiode van de patiënten die deelnamen aan de focus groep discussies: de meeste patiënten hadden al meer dan 10 jaar RA en waren gediagnosticeerd in een tijd waarin niet veel effectieve behandelingen beschikbaar waren. Zij hebben daardoor veel pijn en beperkingen ervaren, inclusief permanente beschadiging van de gewrichten. Tegenwoordig kunnen patiënten die zich presenteren met ontstekingen en zwellingen in enkele gewrichten snel herkend worden als RA patiënten (of RA patiënten in spé) en worden dan ook direct effectief behandeld.

Desondanks laten de resultaten van de focus groep discussies zien dat patiënten met agressieve RA zeker bereid zijn om tijdelijk veel pillen en prednisolon te nemen als dit hun functioneren en prognose kan verbeteren.

Belangrijk voor reumatologen bleek ook het gebrek aan wetenschappelijke vergelijking tussen COBRA therapie en hun huidige voorkeursbehandeling (methotrexaat (MTX) met een eventuele overbrugging met laag gedoseerd prednisolon). Buiten de context van dit proefschrift is recentelijk een trial gestart in Amsterdam (de zogenaamde COBRA “light” studie) om te kijken of de originele COBRA therapie dan wel een light-versie met lager gedoseerde prednisolon, hoger gedoseerde MTX en zonder sulfasalazine (SSZ) te prefereren is.

11-jaar follow up van het COBRA cohort (Hoofdstukken 1.3 & 1.4)

Reumatologen gaven ook aan bezorgd te zijn over de lange termijn effecten van het gebruik van een tijdelijke hoge dosis prednisolon. Om dit effect te onderzoeken hebben we het originele COBRA cohort 11 jaar na de trial opnieuw onderzocht. Dit onderzoek liet zien dat er tussen de twee behandelgroepen geen echte verschillen waren die toegeschreven konden worden aan de oorspronkelijke therapie. De sterfte in de COBRA groep was numeriek lager, en het optreden van cardiovasculaire aandoeningen en andere comorbiditeiten was gelijk in beide groepen. De prevalentie van hypertensie en diabetes mellitus was verhoogd, hoewel de hypercholesterolemie-prevalentie verlaagd was. De prevalentie van osteoporose was ook vrijwel gelijk. Na 10 jaar behandeling naar inzicht van de eigen reumatoloog waren de voordelen van behandeling met COBRA therapie op de ziekte (vertragende in de snelheid van radiologische progressie) nog steeds zichtbaar, en de vertraging van radiologische schade is mogelijk nog steeds door, afhankelijk van de manier waarop omgegaan wordt met missende data. Helaas krijgt iedere studie met een lange follow up duur te maken met uitval van patiënten. In onze studie vielen meer SSZ-patiënten uit dan COBRA-patiënten, en degenen die uitvielen in de SSZ groep hadden ook nog eens een slechtere prognose dan de uitvallers in de COBRA groep. Lineaire imputatie van missende data (het toevoegen van ontbrekende data op basis van een lineair voorspellingsmodel) gebaseerd op de progressiesnelheid van iedere individuele patiënt gaf ons de beste schatting van het werkelijke verschil in progressiesnelheid tussen beide groepen. Imputatie van missende data kan echter gemakkelijk vertekening veroorzaken en moet met grote voorzichtigheid worden toegepast. Een veel gebruikte methode is het nemen van de laatst beschikbare waarneming en deze imputeren op ieder volgend missend moment. In ons geval zou deze methode een totale stop van de progressiesnelheid betekenen voor alle missende data, die daarbij nog eens onevenredig over de behandelgroepen verdeeld waren. Lineaire imputatie van
missende data veronderstelt een lineaire relatie van progressie over de tijd wat ook niet voor iedere patiënt zal kloppen. Echter, de vertekening die ontstaat door de selectieve uitval is ook onacceptabel. Daarom hebben we gekozen voor het presenteren van twee modellen: ten eerste een model met selectieve uitval waarin geen verschil in progressiesnelheid is tussen de groepen, hoewel de COBRA groep op ieder moment 4 Sharp/van der Heijde punten onder de SSZ groep ligt; en ten tweede een model met lineaire imputatie van ontbrekende data waarin de COBRA groep een significante vertraging van de gewrichtsschade heeft in vergelijking met de SSZ groep. Samenvattend hebben we in hoofdstuk 1.3 laten zien dat COBRA therapie net zo veilig is als andere antireumatische geneesmiddelen en mogelijk na 11 jaar nog steeds voordeel biedt boven monotherapie.

De lange, gestructureerde dataverzameling bij het COBRA cohort gaf ons de mogelijkheid om voorspellende factoren van lange termijn uitkomsten te bestuderen. Factoren die op baseline worden gemeten en een voorspellende waarde hebben voor de ziekte-uitkomst op 11 jaar zijn zeer belangrijk, omdat zo de mogelijkheid ontstaat om patiënten met een slechte prognose in een vroeg stadium van de ziekte te selecteren. Uit eerder onderzoek in de COBRA dataset bleek de voorspellende waarde van botmarkers die de bot- en kraakbeenafbraak in het lichaam reflecteren, en bij RA patiënten resulteren in ernstige gewrichtsschade. In eerder onderzoek hebben we laten zien dat de baseline urine waarden van C-terminal cross linking type-I en type-II collageen (CTX-I en CTX-II) en de CTX-II respons na 3 maanden therapie voorspellend zijn voor een verhoogd risico op radiologische progressie na 5 jaar5,6. Een andere marker voor botverlies (of beter gezegd, voor osteoclast activiteit) is de ratio tussen osteoprotegerine (OPG) en receptor activator van nuclear factor-κB ligand (RANKL). In eerder onderzoek van follow up data van de COBRA trial hebben we laten zien dat een lage baseline OPG:RANKL-ratio bij vroege patiënten vóór de start van een behandeling radiologische schade kan voorspellen7. In hoofdstuk 1.4 laten wij zien dat CTX-I, CTX-II en RANKL:OPG zeer sterke, onafhankelijke predictoren zijn van jaarlijkse radiologische schade over 11 jaar. Door patiënten met een hoge baseline waarde van CTX-I, CTX-II en een lage RANKL:OPG ratio vroeg op te sporen, kan de ernst van het verloop van de ziekte beter worden ingeschat en de behandeling hierop worden afgestemd. Een tekortkoming van deze studie is dat anticyclic citrillunated peptide (anti-CCP) in het COBRA cohort niet is gemeten, terwijl dit een van de sterkste predictoren van radiologische schade is8-11. De voorspellende waarde van CTX-I, CTX-II en de RANKL:OPG ratio moet verder onderzocht worden in een multivariaat model waarbij anti-CCP ook wordt meegenomen. Daarnaast is er wetenschappelijk bewijs uit dierstudies dat het remmen van RANKL kan leiden tot het voorkomen van nieuwe erosies12.

In deze context is het van belang om het effect van verschillende behandelaanpakken te onderzoeken, gelijkzijdig met het ontstaan van nieuwe erosies.

**Ontwerp en testdraaien van een implementatie plan (Hoofdstuk 1.5)**

Nadat we alle aspecten van de COBRA therapie vanuit het perspectief van zowel de reumatoloog als de patiënt hadden geëvalueerd, hebben we een implementatieplan ontwikkeld. De vraag die centraal stond in dit praktische gedeelte van ons onderzoek was: 'Hoe kunnen we het gebruik van de COBRA therapie in de praktijk door zowel patiënten als reumatologen en reumaverpleegkundigen gemakkelijker en prettiger maken?' Veel aanwijzingen voor verbetering van het gebruiksgemak in de dagelijkse praktijk waren naar voren gekomen tijdens de focus groep discussies. Zo vonden reumatologen de COBRA therapie ingewikkeld en tijdgevend om voor te schrijven. Ook werd verondersteld dat patiënten misschien bezwaar zouden hebben tegen het gebruik van veel pillen of prednisolon. Om het obstakel van tijdgebrek en specifieke informatievoorziening voor reumatologen weg te nemen
hebben we patiëntinformatie materiaal ontwikkeld met daarin visuele hulpmiddelen voor uitleg van de therapie, duidelijke tabellen waarin de inname van de verschillende tabletten wordt weergegeven, en voorgedrukte recept-stickers om het voorschrijfproces te versnellen. Ook hebben we de resultaten van het focus groep onderzoek verspreid, waarin patiënten uitleggen dat het tijdelijk gebruik van een groot aantal pillen of prednisolon voor hen acceptabel is, mits daarmee de klachten snel afnemen en de prognose verbetert. Om patiënten zoveel mogelijk op hun gemak te stellen bij het gebruik van de COBRA therapie, hebben we het patiëntinformatie materiaal voorzien van een interview met een fictieve nieuwe RA patiënt die haar gevoelens uit na het horen van de diagnose RA en het starten met COBRA therapie. De inhoud van dit interview kwam voort uit quotes van patiënten tijdens de focus groep discussies en is gemaakt om patiënten die starten met de therapie een positieve start te geven. Vervolgens hebben we een groep van gemotiveerde reumatologen en reumaverpleegkundigen gevraagd om hun patiënten COBRA therapie voor te schrijven met behulp van het verspreide materiaal. Zowel reumatologen, patiënten als reuma verpleegkundigen hebben het materiaal geëvalueerd en gaven allemaal zeer positieve beoordelingen.

De website, waarop al het patiëntinformatie materiaal, maar ook de wetenschappelijke publicaties en dit proefschrift zijn te downloaden, is online op: www.cobratherapie.nl zodat COBRA therapie wereldwijd kan worden gebruikt.

Om de impact van onze COBRA implementatie studie te onderzoeken kunnen digitale apotheek hulp bij het bestuderen van de toename van het aantal specifieke recepten. Wij zijn van plan om het aantal voorschriften van de COBRA therapie ruim voor de start en ruim na de afsluiting van deze studie te meten, door de digitale apotheek de vraag voor te leggen hoe vaak de combinatie SSZ, MTX en prednisolon bij de diagnose RA is voorgeschreven. Daarbij is het van belang om dat ruim voor de start van deze studie en ruim na publicatie van dit proefschrift te meten, zodat de resultaten niet vertekend zijn door een tijdelijke aandacht voor COBRA therapie.

**SECTIE II: COBRA-CTX STUDIE**

Parallel aan de hierboven beschreven implementatie studie groeide het aantal publicaties over de effectiviteit van monitoringsstrategieën. Dit maakte ons nieuwsgierig naar de voordelen van een geïntensiveerde COBRA therapie in combinatie met een monitoringsstrategie. Verschillende studies hebben de effectiviteit aangetoond van sturing op de DAS (disease activity score, een samengestelde maat voor ziekteactiviteit, zie introductie): de BeSt studie vergelijkt vier behandelstrategieën die allen gestuurd worden op de DAS; alle vier de behandelstrategieën bleken zeer effectief in combinatie met de strikte monitoring van de DAS, hoewel de twee combinatiestrategieën superieur waren door de zeer snelle onderdrukking van ontstekingen en het vertragen van de radiologische schade\(^{13,14}\). De TICORA trial is een ander goed voorbeeld van de voordelen van monitoringsstrategieën op ziekteactiviteit. In deze trial behaalde 65% van de patiënten die gestuurd werden een DAS remissie, tegenover 16% van de patiënten die gebruikelijke zorg kregen. De monitor- groep had ook een 6 keer hogere odds op het behalen van een goede EULAR respons in vergelijking met de groep die gebruikelijke zorg kreeg\(^{15}\). De eerste en meest effectieve trial die een combinatietherapie bestudeerde, gecombineerd met een monitoringsstrategie was de FIN-RACo trial, waarin 68% van de patiënten een DAS28 remissie bereikte\(^{16}\). Deze trials hebben allemaal gestuurd op basis van de DAS, terwijl verschillende recente studies suggereren dat radiologische progressie mogelijk gedeeltelijk onafhankelijk is van ziekteactiviteit. Dit heeft geled tot de hypothese dat klinische ziekteactiviteit en radiologische progressie worden aangestuurd door verschillende ziekteprocessen\(^{17}\). Hoewel er verschillen
in mening over bestaan is gesuggereerd dat een ontkoppeling van radiologische progressie en ziekteactiviteit ontstaat bij patiënten zonder klinische reactie maar wel een vertraging in radiologische progressie laten zien, en andersom dat bij patiënten in klinische remissie de radiologische progressie door gaat. In deze setting kan sturing op een meer directe marker van radiologische progressie wellicht voordeel opleveren.

De COBRA-CTX pilot trial (Hoofdstukken 2.1 & 2.2)

Zoals reeds beschreven in hoofdstuk 1.4 is radiologische schade bij patiënten met reumatoïde artritis het gevolg van bot- en kraakbeenafbraak. Om de mate van bot- en kraakbeenafbraak te meten zijn biologische markers geïdentificeerd. Twee van zulke markers zijn geïntroduceerd in hoofdstuk 1.4: CTX-I en CTX-II. In data van de COBRA trial is aangetoond dat CTX-II radiologische schade over 5 jaar kan voorspellen. CTX-II kon dit beter dan IgM reumafactor (RF), baseline schade en ziekteactiviteit (gemeten als bezinkingsniveau van de erytrocyten). In dit onderzoek kon ook een niveau van CTX-II worden bepaald waaronder geen verdere radiologische progressie optrad; een waarde die gelijk is aan die van gezonde controles. Naar aanleiding van deze resultaten formuleerden wij de hypothese dat CTX-II een betere marker voor sturing van geïntensiveerde behandeling zou kunnen zijn dan ziekteactiviteit gemeten met behulp van de DAS. Om de haalbaarheid van een studie met deze hypothese te onderzoeken hebben we een pilot trial opgezet waarin monitorsingsstrategieën op basis van herhaalde metingen van de DAS, dan wel van CTX-II excretie werden vergeleken. Patiënten werden gerandomiseerd voor monitorsingsstrategie waarbij de therapie geïntensiveerd werd indien de streefwaarde voor de DAS dan wel de CTX-II niet werd gehaald. Om er zeker van te zijn dat alle patiënten effectief werden behandeld kreeg iedereen een geïntensiveerde variant van de COBRA therapie inclusief hydroxychloroquine vanaf baseline, verhoging van de dosis MTX indien de streefwaarden niet werden bereikt binnen 8 weken en introductie van infliximab wanneer de streefwaarden niet werden bereikt binnen 21 weken.

Deze intensieve behandeling in combinatie met een strikte monitorsingsstrategie bleek haalbaar en resulteerde in een ongekend hoog percentage patiënten dat een DAS remissie behaalde (90%). Echter, een CTX-II remissie werd minder gemakkelijk behaald en was onafhankelijk van meer geïntensiveerde behandeling in de CTX-groep. Het hoge remissiepercentage in onze studie wordt het best verklaard door het intensieve behandleschema. In vergelijking met eerdere trials werden meer geneesmiddelen, in hogere doseringen gegeven en de behandeling kon al na 8 weken geïntensiveerd worden.

In deze studie lieten we tevens zien dat intensieve conventionele DMARD therapie met een hoge initiële dosis prednisolon volgens het COBRA schema een snelle daling van zowel RF als anti-CCP in serum van ruim 50% tot gevolg heeft. In de COBRA trial en diverse andere studies werd ook een snelle daling van RF gezien, maar zo’n snelle en forse daling van anti-CCP tijdens behandeling van vroege RA patiënten is nog niet eerder beschreven. De aanwezigheid van RF en anti-CCP in een vroeg stadium van de ziekte wordt geassocieerd met ernstiger radiologische progressie. Het sturen van de behandeling op basis van anti-CCP naast ziekteactiviteit zou de effectiviteit van behandelsstrategiën die gericht zijn op het voorkomen van schade en verlies van functie verder kunnen verhogen.
reumatoïde artritis patiënten. Deze resultaten pleiten uiteraard voor toepassing in een grote klinische trial, waarin het effect van sturing van CTX-II op radiologische progressie en de effectiviteit en veiligheid van de behandelstrategie verder onderzocht kan worden.

SECTIE III: ACR/EULAR/OMERACT REMISSIE INITIATIEF

Een derde belangrijke ontwikkeling die beschreven wordt in dit proefschrift is de groeiende verwarring rondom het concept van remissie in RA. In de hierboven beschreven COBRA-CTX studie lieten we zien dat 90% van de patiënten een DAS28 remissie behaalde, maar slechts 45% van de patiënten behaalde remissie volgens de definitie van the American college of Rheumatology (ACR). Recente studies die kijken naar remissie, gedefinieerd op verschillende manieren, worden allemaal met hetzelfde probleem geconfronteerd: het gebruik van verschillende definities om remissie te meten leidt tot verschillende percentages behaalde remissies waardoor het vergelijken van trials onderling onmogelijk wordt\textsuperscript{34-36}. 

Het definiëren van remissie in reumatoïde artritis (Hoofdstukken 3.1 &3.2)

De ACR, EULAR en het OMERACT initiatief hebben besloten de handen ineen te slaan om toe te werken naar een uniforme definitie van remissie met optimale eigenschappen in klinische trials en haalbaarheid in de klinische praktijk (hoewel deze definities wellicht niet identiek zullen zijn). Een commissie van internationale experts op het gebied van remissie in RA werd uitgenodigd om te discussiëren over de onderzoeksagenda. Dit resulteerde in een eerste afbakening voor een toekomstige remissiedefinitie zoals beschreven in hoofdstik 3.1; experts waren het erover eens dat een strikte definitie nodig is, in tegenstelling tot de DAS28 definitie van remissie waarbij gewrichten in de voeten niet worden meegenomen\textsuperscript{37}. Verder vond de commissie dat een mogelijke remissiedefinitie gevalideerd moet worden tegen radiologische progressie en functie: een goede definitie moet in staat zijn te differentiëren tussen patiënten waarbij de progressie stopt danwel doorgaat en het functioneren voor- dan wel achteruit gaat. Omdat het onbekend was in hoeverre de huidige remissiedefinities in staat zijn om hiertussen te differentiëren hebben we de literatuur ernaar gezocht. Hoofdstuk 3.2 laat zien dat patiënten die remissie behalen, ongeacht de remissiedefinitie, een beter verloop van radiologische progressie en fysiek functioneren hebben, vergeleken met patiënten die geen remissie behalen. Ook kwam de reeds eerder beschreven complexiteit rondom remissie en radiologische progressie opnieuw naar voren: patiënten in klinische remissie kunnen nog steeds radiologische progressie vertonen terwijl omgekeerd, met name bij patiënten die met biologicals behandeld werden, ziekteactiviteit aanwezig kan zijn terwijl progressie is gestopt. Dit suggereert een verschil in pathologie tussen ziekteactiviteit en radiologische progressie. Er is meer onderzoek nodig naar deze zogenaamde ‘ontkoppellingshypothese’ en het verschil in respons op DMARDs versus biologicals. Op dit moment worden datasets vanuit de hele wereld geanalyseerd om de variabelen met de beste meeteigenschappen te identificeren als mogelijke kandidaten voor een nieuwe remissiedefinitie.

TOEKOMSTPERSPECTIEF

COBRA therapie is effectief, veilig en met behulp van het juiste materiaal goed te gebruiken in de klinische praktijk door zowel patiënten als reumatologen en reumaverpleegkundigen. Het zou verstandig zijn om COBRA therapie nationaal te implementeren als voorkeursbehandeling voor patiënten met een vroege, agressieve reumatoïde artritis, niet alleen vanuit een medisch perspectief, maar wellicht ook vanuit een economisch en patiënt perspectief. Omdat COBRA therapie bestaat uit een combinatie van goedkope, generieke geneesmiddelen is het een zeer kosteneffectieve behandeling. Patiënten zouden belang kunnen hebben bij implementatie van COBRA therapie omdat dit hen een betere prognose geeft in vergelijking met monotherapie. Daarom is het aan te raden dat reumatologen
wereldwijd hun vroege, agressieve RA patiënten adviseren met COBRA therapie te starten. Indien de respons op de therapie niet zo goed is als gewenst kan snel worden overgestapt naar een biological in combinatie met MTX. Dan is ook meteen aan de voorwaarde voldaan dat de patiënt eerst op twee DMARDs moet hebben gefaald alvorens met een biological te starten. Met deze strategie worden RA patiënten snel, effectief en kosteneffectief behandeld en wordt de kans op het snel terugkrijgen van functionaliteit groter, en de kans op het voorkomen van permanente radiologische schade kleiner.

Wanneer effectieve therapie wordt gecombineerd met het frequent meten van de ziekteactiviteit, kan de behandeling van patiënten die niet goed reageren snel worden aangepast. We hebben laten zien dat een grote trial haalbaar en noodzakelijk is om enerzijds de effectiviteit en veiligheid van een gomodificeerd COBRA schema verder te onderzoeken en anderzijds de effectiviteit van een monitoringsstrategie op basis van botmarkers verder te onderzoeken. Ook hebben we laten zien dat we wellicht niet alleen moeten focussen op CTX-II, maar dat de beïnvloeding van de RANKL:OPG ratio misschien nog belangrijker is voor het onderdrukken van radiologische progressie. Meer onderzoek is nodig naar de respons van de RANKL:OPG ratio op effectieve behandeling. Als deze marker net als CTX-II sterk reageert tijdens effectieve behandeling kan een toekomstige trial van verschillende monitoringsstrategieën hun onafhankelijke of gezamenlijke rol als indicatoren voor radiologische progressie ophelderen. De respons van RANKL:OPG op effectieve behandeling tijdens onze COBRA-CTX pilot trial staat daarmee hoog op onze eigen onderzoeksagenda. In de tussentijd heeft onderzoek duidelijk laten zien dat sturing op de DAS een positieve invloed heeft op het verloop van de ziekte. Daarom is implementatie van deze monitoringsstrategie van groot belang en zou zo snel mogelijk standaard moeten zijn in alle ziekenhuizen waar RA patiënten behandeld worden.

Ontwikkeling van een nieuwe definitie voor remissie is een grote uitdaging, gezien de onzekerheid omtrent de pathologische processen van botafbraak en de optimale manier om ziekteactiviteit te meten. Ondanks deze onzekerheden laat ons onderzoek zien dat het behalen van remissie, volgens welke definitie dan ook, een betere ziekte-uitkomst geeft op de lange termijn. Daarom is het aan re raden om door te gaan met het sturen op remissie op een manier die haalbaar is in de setting waar de zorg wordt verleend, maar het werk van de commissie van remissie-experts in het vizier te houden. De bundeling van krachten van zowel de ACR, EULAR als het OMERACT initiatief bieden de beste basis voor het ontwikkelen en implementeren van een nieuwe maat voor remissie in zowel klinische trials als de klinische praktijk.
BELANGRIJKSTE BEVINDINGEN

- COBRA therapie is niet erg populair bij reumatologen omdat zij het een ingewikkelde therapie vinden, het veel tijd vinden kosten om voor te schrijven en denken dat patiënten het niet willen gebruiken.

- Patiënten hebben geen bezwaar tegen het gebruik van een agressieve combinatie therapie inclusief prednisolon of een grote hoeveelheid pillen, zolang het van tijdelijke aard is en hun prognose ermee verbetert.

- COBRA therapie is net zo veilig als andere antireumatische geneesmiddelen en biedt mogelijk na 11 jaar nog steeds voordeel boven monotherapie.

- Op maat gemaakt informatie materiaal voor reumatologen, patiënten en reumaverpleegkundigen faciliteert het gebruik van COBRA therapie in de klinische praktijk.

- Markers voor bot- en kraakbeenafbraak, gemeten voor start van een behandeling, zijn sterke predictoren van jaarlijkse radiologische progressie.

- Een trial met geïntensiveerde COBRA therapie en een sturingsstrategie op basis van botmarker CTX-II met als doel toekomstige radiologische schade zoveel mogelijk te voorkomen, is haalbaar. Bovendien is het opzetten van een dergelijke trial van belang vanwege het hoge percentage patiënten dat remissie behaalt en de scherpe daling in reumafactor en anti-CCP gevonden in onze pilot trial.

- Huidige definities van remissie zijn in staat om verbetering van lange termijn uitkomsten te voorspellen, maar de definitie van het begrip remissie in RA is op dit moment niet bruikbaar. Een internationale commissie van remissie-experts heeft als doel hier verandering in te brengen.
REFERENCES


Lilian van Tuyl was born on the 3rd of March 1981 in Wageningen. She received her VWO diploma in 1999 at the Hendrik Pierson College in Zetten. After a summer course in physics, she starts the study Nutrition & Health at Wageningen University. In 2002, she is selected for a 4 month internship with Unilever Bestfoods in Jakarta, Indonesia, where she studies the nutrition and health situation of vulnerable groups of the population. Returning to The Netherlands, she starts her first research project at the department of Dietetics in the Julius Center of the University Medical Center of Utrecht. Here she studies the change in bodyweight and body composition after obesity treatment. Her second research project in September 2003 is with Helen Keller International in Kathmandu, Nepal, where she studies breastfeeding and complementary feeding practices and beliefs of two rural ethnic groups. After an inspiring journey through South and South-East Asia, she receives her Master of Science diploma in September 2004.

In January 2005, she starts her PhD research at the department of Epidemiology & Biostatistics and the department of Rheumatology of the VU University Medical Center, under the supervision of Prof Dijkmans, Prof Boers, Prof Lems and Dr Voskuyl. At the same time, she starts the postgraduate Epidemiology programme (POE), for which she receives her Master of Science diploma from the VU University, Amsterdam, in May 2008. As of January 2009, she works as a post doc researcher and research coordinator at the department of Rheumatology of the VU University Medical Center.


DANKWOORD

Alle patiënten, reumatologen en reuma verpleegkundigen die hebben geholpen met het opzetten, uitvoeren en rapporteren van het onderzoek beschreven in dit proefschrift: bedankt!

Een aantal personen wil ik in het bijzonder bedanken:


Maarten, jouw enthousiasme werkt aanstekelijk. Ik heb je erg dankbaar voor de energie die je in dit onderzoek hebt gestoken. Ondanks je drukke schema ben je altijd bereid om samen een grafiek tot in de puntjes te perfectioneren of om mij klaar te stomen voor een presentatie op een congres. Ik heb heel veel van je geleerd en ben blij met een begeleider die zo betrokken is als jij bent.

Alexandre, door jouw vermogen om structuur en prioritering in mijn dagelijkse werkzaamheden aan te brengen kwam ik iedere week weer positief gestemd met een plan van aanpak uit het ziekenhuis. Bedankt voor je steun en vertrouwen in mij, ook in mijn nieuwe functie.

Willem, jij zit boordevol nieuwe ideeën en weet mij elke keer weer te enthousiasmeren voor een nieuw artikel of project, zo ook voor hoofdstuk 1.4, bedankt! Gelukkig zit ik tegenwoordig wat dichterbij en kunnen we uitgebreid brainstormen over nieuwe uitdagingen.

Ben, onze maandelijkse besprekingen om de vorderingen van dit proefschrift te bespreken gaven mij de motivatie om extra hard te werken, zodat we weer een artikel van de lijst konden afvinken. Bedankt voor de goede begeleiding en voor het vertrouwen in mij als postdoc onderzoeker en onderzoekscoördinator op de afdeling reumatologie.

Anne Marie: jouw sociaal-psychologische kijk op het onderzoek was vaak verfrissend en ik wil je bedanken voor de leuke en leerzame tijd.

Pit: mede dankzij jouw inzet is de CTX pilot trial een succes geworden. Bedankt voor je steeds rake feedback en je betrokkenheid bij mijn promotie onderzoek.

David, George and Josef: thank you for giving me the opportunity to join your executive remission committee and enriching this thesis with section III. I have learned a lot from working with you and am very curious what the new definition for remission in RA will be.

Collega's van de (voormalige) afdeling KEB: ik heb een erg leuke tijd gehad op de afdeling, ‘de Lilian,’ en VT Wonen herinneren mij nog iedere maand aan de lieve collega’s aan de overkant, bedankt! Mijn kamergenootjes in PK 159 door de jaren heen: Daphne, Ivo, Mariele, Sietse en Femke, bedankt voor jullie vriendschap. Anne Marie, jij stond altijd klaar voor hulp, advies of een praatje, wat was het saai op de gang als jij met vakantie was, bedankt voor alles! Maarten en Bernard, bedankt voor jullie sturing als leidinggevers, en de mogelijkheid mijn MSc-diploma epidemiologie te halen.

Collega's van de afdeling reumatologie in VUmc en Jan van Breemen, bedankt voor de warme ontvangst op jullie afdeling en de gezellige momenten op congressen. Tijdens de 4 jaar van mijn promotie onderzoek heb ik jullie nauwelijks gezien, maar ik vind het erg leuk dat ik jullie de afgelopen maanden beter heb leren kennen.

De lees / promotie commissie bestaande uit Prof dr Hazes, Prof dr Bijlsma, Prof dr Twisk, Prof dr van der Heijde, Prof dr Geusens, Prof dr van Kuijk, Prof dr Lips en dr Hulscher, wil ik bedanken voor het beoordelen van dit proefschrift.
Vrienden en familie, bedankt voor jullie interesse en alle gezelligheid naast het werk. En in het bijzonder: Elise, Marieke en Angelique, veel succes met jullie proefschriften!

Paranimfen Winanda en Eva: bedankt voor jullie toegezegde steun tijdens de verdediging van dit proefschrift. Met jullie naast me durf ik het wel aan.

Carolien & Koen, jullie zakelijke instinct tijdens gesprekken aan de keukentafel heeft mij meerdere malen inspiratie gegeven om problemen op te lossen. Carolien, bedankt voor je oprechte interesse in mijn werk en voor het doorspitten van dit proefschrift. Mariette, jouw bijdrage als invoerder van data heeft mij vele uurtjes ploeteren bespaard, bedankt! Ik ben blij dat de kantine van het VUmc zo’n aantrekkingskracht op je heeft; ik hoop dat we er nog regelmatig gezellig zullen lunchen of koffiedrinken.

Papa, bedankt voor het goede voorbeeld. Ik denk dat het jouw verre reizen waren die mijn allereerste interesse wekten voor het vak van onderzoeker; ondertussen weet ik wel beter 😊. Ik hoop dat ik net zo goed in dit vak mag worden als jij bent. Mama, zonder jou stond dit proefschrift, in het bijzonder de Nederlandse stukken, vol met de wel bekende Lilian-spelfouten. Bedankt voor je grondige inspectie en je onvoorwaardelijke steun en liefde de afgelopen jaren.

Samadh, mijn grote liefde, jij maakt het leven mooi. Dankzij jou ben ik aan dit proefschrift begonnen en dankzij jouw ontwerpen ziet alles eruit zoals ik het graag wil hebben, dankjewel, ook voor alles dat ik hier niet vertel. En nu, op naar ons volgende avontuur!