Effective treatment for rapid improvement of both disease activity and self-reported physical activity in early rheumatoid arthritis

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Objective: To investigate the longitudinal relationship between disease activity and self-reported physical activity (PA) in patients with early rheumatoid arthritis during the first year of treatment with combination therapy.

Methods: PA was measured with the Short QUestionnaire to ASsess Health-enhancing physical activity (SQUASH) at baseline, 13 weeks, 26 weeks, and 52 weeks after start of treatment in context of the COBRA-light trial. The reported PA classified patients as meeting or not meeting the World Health Organization (WHO) PA guideline (cut off: 150 minutes of moderate-to-intense activity per week). Other measurements included the Disease Activity Score (DAS). Since both treatment arms showed equal treatment effect, these were analysed as one group with simple before-after analyses and generalized estimating equations (GEE).

Results: In these analyses, 140 patients (86% of the trial population; 66% women, mean age 52 years) with complete data were included. At entry, 69% of the patients met the WHO PA guideline, increasing to 90% at week 13, and remaining stable at 89% after one year (p<0.001). Mean DAS improved from 4.0 to 1.8 during the first year of treatment (p<0.001). In GEE analyses, DAS decreases were significantly associated with PA increases (p=0.008). Patients with clinically relevant responses (expressed as DAS remission, EULAR good or ACR70 response) showed higher PA levels compared to non-responders, regardless of the definition of response, for both the WHO and Dutch PA guideline.

Conclusion: Early RA patients using combination therapy improved both disease activity and physical activity, a beneficial effect persisting for at least one year.
Introduction
Extensive research has demonstrated multiple benefits of regular physical activity (PA) such as reduced incidence of osteoporotic fractures, decreased mortality and morbidity of cancer, cardiovascular disease and other chronic diseases, and improved psychological well-being.1 In patients with rheumatoid arthritis (RA), a chronic, inflammatory joint disease associated with osteoporotic fractures and increased risk of cardiovascular events, regular PA might have additional health benefits such as positive effects on aerobic capacity, muscle strength and muscle function without exacerbating disease activity and pain.2,3

The World Health Organization (WHO) recommends adults to spend at least 150 minutes per week on moderate to intense physical activities.4 This recommendation is often difficult to meet for RA patients, especially during exacerbations of disease. Combination therapy, including the original COBRA-scheme (’COmbinatietherapie Bij Reumatoïde Artritis’, combination therapy for rheumatoid arthritis) from 19975 and the recently developed COBRA-light therapy,6,7 has proven to be a successful treatment for RA, reducing disease activity and improving physical functioning. Both therapies combine prednisolone and methotrexate (MTX), the COBRA treatment also includes sulfasalazine (SSZ). The effect of combination therapy on PA has not been studied before.

The relation between disease activity and PA in RA patients has been described in some cross-sectional studies,8,9 but no prospective study on this relation in early RA patients has been performed during the last decade. Therefore, the purpose of this study was to investigate the longitudinal relationship between disease activity and PA in early, active RA patients.

Patients and methods

Study design and study population
This study was part of the larger multicenter COBRA-light trial,6,7 which assessed the noninferiority of COBRA therapy versus ‘COBRA-light’ therapy on clinical and radiologic outcomes in early RA. In brief, COBRA therapy (prednisolone 60 mg/day, tapered to 7.5 mg/day in 7 weeks, MTX 7.5 mg/week and SSZ 2 g/day) was compared with COBRA-light therapy (prednisolone 30 mg/day, tapered to 7.5 mg/day in 9 weeks and MTX escalated to 25/mg week in 9 weeks). Patient-selection criteria, the randomisation process and study design have been reported previously.6 Medical ethics committees at each participating center approved the protocol; patients gave written informed consent before inclusion, and the study was conducted in accordance with the Declaration of Helsinki/Good Clinical Practice. Patients with missing data on PA or disease activity at one or more visits (n=22) were excluded from the analyses of this sub study on PA.
Outcome measures

Patients visited their study center at diagnosis (baseline) and after 13, 26, and 52 weeks. Primary outcome measure of the study was the Disease Activity Score in 44 joints (DAS); results were also expressed as percentage patients in DAS remission (DAS<1.6), and as percentage patients having an EULAR good response and ACR70 response, as specified by the EULAR/ACR recommendations for reporting disease activity in clinical trials. Physical functioning was assessed with the Health Assessment Questionnaire (HAQ).

PA was measured with the Short QUestionnaire to ASsess Health-enhancing physical activity (SQUASH). In the SQUASH questionnaire, patients were asked to recall which PA was performed during the past week and comprises questions about commuting activities, activities at work and school, household activities, leisure time and sports activities. Patients were asked to fill in how many days per week and how many hours per day were spent executing the specific activity, allowing calculation of the total time per week spent on PA. The intensity of each activity is depicted by its metabolic equivalent (MET), the ratio of work metabolic rate to a standard resting metabolic rate. One MET is comparable to the resting metabolic rate obtained during quiet sitting, walking has a MET of 3.5, cycling has a MET of 5.0 and running has a MET of 8.0.

The WHO guideline for PA recommends adults to spend at least 150 minutes on moderate-to-intense PA throughout the week, with a minimally required intensity of 3.0 MET. The Dutch guideline for PA recommends adults to spend at least five days per week 30 minutes per day in moderate-to-intense activity. The minimally required intensity of PA of the Dutch guideline depends on age: adults younger than 55 years require a minimum MET value of 4.0, older adults require a minimum value of 3.0 MET.

Missing, impossible or unrealistic answers on the SQUASH questionnaire were adjusted according to the SQUASH data handling instructions and protocolized assumptions of the researchers. In total 304 out of 18480 (1.7%) answers were manually adjusted. We performed sensitivity analyses to compare the crude and manually adjusted data.

Statistical analysis

The COBRA and COBRA-light therapy are an equally effective treatment for early RA. Therefore, patients of both treatment arms were analysed as one group in this sub study on PA. Data are presented as mean (standard deviation), or as median [interquartile range] in case of skewed data, unless otherwise specified.

Paired t-tests, Wilcoxon and McNemar tests evaluated differences within subgroups over time, where appropriate. Chi Square tests evaluated differences in proportions between subgroups at one time point. Generalised Estimating Equation (GEE) was used to assess differences of disease activity, PA and the WHO-ILAR core set over time, correcting for repeated measures. Skewed data was first log transformed, after which GEE analyses were performed.
We hypothesised that patients with decreasing disease activity would increase PA over time. Accordingly, we analysed the longitudinal association between PA (% patients meeting the PA guideline) and disease activity (DAS) for both the WHO and Dutch PA guideline. We performed logistic GEE analysis as PA (meeting the WHO or Dutch PA guideline) was a dichotomous outcome. The following variables were stepwise evaluated as confounding or effect modifying factors: age, sex, disease duration, morning stiffness, patient assessment of pain and body mass index. An odds ratio >1.0 indicates that exposure is associated with a higher odds of outcome and an odds ratio <1.0 indicates that exposure is associated with a lower odds of outcome. All statistical analyses were performed with IBM SPSS Statistics, release 20.0 (SPSS Inc, Chicago, Illinois, United States). P-values<0.05 were considered significant; no adjustments were made for multiple comparisons.

Results

Disease activity and physical functioning over time
In this study, 140 early RA patients (86% of trial population; 66% women, mean age 52 years, range 21 - 83 years) had complete data and were included for analyses (Table 1). During the first year of diagnosis, mean DAS score decreased significantly from 4.0 at baseline, to 2.0 after 13 weeks and 1.8 after 52 weeks (GEE over time: p<0.001) (Figure 1). Median HAQ score, indicator of physical functioning, improved significantly from 1.25 at baseline to 0.44 after 13 weeks and 0.50 after 52 weeks (GEE over time: p<0.001).

Physical activity over time
At baseline, 69% of the patients met the WHO PA guideline, increasing significantly to 90% at 13 weeks and stabilizing thereafter: 89% after 52 weeks (GEE over time: p<0.001) (Table 1 and Figure 1). Median moderate-to-intense PA minutes per week increased significantly from 378 minutes at baseline to 570 at 13 weeks, 523 after 26 weeks, and 540 minutes after 52 weeks (GEE over time: p<0.001). This increase was driven by a significant increase in PA during leisure time (walking (p=0.008), cycling (p=0.002) and gardening (p=0.032)) and sports activities (p<0.001).

In addition, 59% of the patients met the Dutch PA guideline at baseline, increasing significantly to 81% at 13 weeks and stabilizing thereafter: 82% after 52 weeks (GEE over time: p<0.001). Median moderate-to-intense PA minutes per week increased significantly from 225 minutes at baseline to 420 at 13 weeks, 450 after 26 weeks, and 413 minutes after 52 weeks (GEE over time: p<0.001).

Sensitivity analyses showed no difference between crude and manually adjusted data in all major analyses of PA.
TABLE 1. Patient characteristics including disease activity and physical activity (n=140)

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Week 13</th>
<th>Week 26</th>
<th>Week 52</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female, n (%)</td>
<td>93 (66)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Age at baseline in years, mean (SD)</td>
<td>52 (13)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Disease duration at baseline in weeks, median [IQR]</td>
<td>16 [23]</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>DAS, mean (SD)</td>
<td>4.0 (0.8)</td>
<td>2.0 (1.1)</td>
<td>1.6 (1.1)</td>
<td>1.8 (1.0)*</td>
</tr>
<tr>
<td>HAQ, median [IQR]</td>
<td>1.25 [1.00]</td>
<td>0.44 [1.00]</td>
<td>0.38 [1.00]</td>
<td>0.50 [1.00]*</td>
</tr>
<tr>
<td>Patients meeting the WHO guideline for PA, n (%)</td>
<td>96 (69)</td>
<td>126 (90)</td>
<td>120 (86)</td>
<td>125 (89)*</td>
</tr>
<tr>
<td>Patients meeting the Dutch guideline for PA, n (%)</td>
<td>82 (59)</td>
<td>114 (81)</td>
<td>108 (77)</td>
<td>115 (82)*</td>
</tr>
<tr>
<td>Morning stiffness duration in min, median [IQR]</td>
<td>¥ 60 [90]</td>
<td>0 [26]</td>
<td>0 [15]</td>
<td>5 [30]*</td>
</tr>
</tbody>
</table>

Data are presented as mean (standard deviation) for normally distributed variables and as median [interquartile range] for non-parametric variables, unless otherwise specified; *All changes were statistically significant (p<0.05) both compared to baseline and expressed as difference over time (GEE analyses), ‡n=120, ¥n=118; DAS = Disease Activity Score, HAQ = Health Assessment Questionnaire, IQR = interquartile range, min = minutes, mm = millimeters, PA = physical activity, SD = standard deviation, VAS = visual analogue scale, WHO = World Health Organization.

FIGURE 1. Change in disease activity and physical activity in early RA patients over time (n=140)

Disease activity data are presented as mean Disease Activity Score (DAS) ± SD, physical activity data are presented as % patients meeting the WHO guideline for physical activity; *significant difference over time in GEE analyses (p<0.05).

**Longitudinal association between disease activity and physical activity**

In logistic GEE analyses, disease activity (DAS) was longitudinal associated with an odds ratio of 0.69 for meeting the WHO PA guideline (p=0.008) (Model 1 in Table 2). In other words: an increase of disease activity was associated with a decrease of PA. Opposing, a decrease of disease activity was associated with an increase of PA.
In addition, disease activity was longitudinal associated with an odds ratio of 0.72 for meeting the Dutch PA guideline (p=0.005), demonstrating a similar but weaker association between disease activity and PA (Model 2 in Table 2).

Both longitudinal associations were significantly influenced by patient assessment of pain and duration of morning stiffness.

### TABLE 2. Logistic GEE model of the longitudinal association between disease activity and physical activity in early RA patients (n=140)

<table>
<thead>
<tr>
<th>Model</th>
<th>Outcome parameter</th>
<th>OR Constant</th>
<th>OR DAS</th>
<th>95% CI</th>
<th>p-value</th>
<th>OR time</th>
<th>Confounder</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 - Crude</td>
<td>WHO PA guideline</td>
<td>22.49</td>
<td>0.57</td>
<td>0.472; 0.691</td>
<td>p&lt;0.001</td>
<td>1.00</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>1 - Adjusted</td>
<td>WHO PA guideline</td>
<td>19.25</td>
<td>0.69</td>
<td>0.525; 0.907</td>
<td>p=0.008</td>
<td>1.00</td>
<td>Patient assessment of pain by VAS (mm)</td>
<td>0.99</td>
</tr>
<tr>
<td>2 - Crude</td>
<td>Dutch PA guideline</td>
<td>10.16</td>
<td>0.62</td>
<td>0.520; 0.728</td>
<td>p&lt;0.001</td>
<td>1.00</td>
<td>Duration of morning stiffness (min)</td>
<td>1.00</td>
</tr>
<tr>
<td>2 - Adjusted</td>
<td>Dutch PA guideline</td>
<td>8.59</td>
<td>0.72</td>
<td>0.569; 0.905</td>
<td>p=0.005</td>
<td>1.00</td>
<td>Patient assessment of pain by VAS (mm)</td>
<td>0.99</td>
</tr>
</tbody>
</table>

CI = confidence interval, DAS = Disease Activity Score, OR = odds ratio, PA = physical activity (meeting the WHO or Dutch PA guideline), VAS = visual analogue scale, WHO = World Health Organization.

### Remission and response to treatment

After 52 weeks, 45% of the patients were in DAS remission (DAS<1.6), 70% of the patients had an EULAR good response and 36% had an ACR70 response. At each individual time point after baseline, responders showed higher PA levels compared to non-responders, regardless of the definition of response, for both the WHO and Dutch PA guideline (data shown in online supplement).

### Discussion

To our knowledge, this is the first study that shows that combination therapy is not only effective in decreasing disease activity, but also improves self-reported physical activity (PA) in early rheumatoid arthritis (RA) patients. This result was shown longitudinally for both continuous (DAS) and binary measures (response criteria).

Our study reported the largest improvement in PA between baseline and 13 weeks, when treatment with prednisolone and MTX (and in the COBRA-group also SSZ) was started and both disease activity (DAS) and functional capacity (HAQ) significantly improved. A small decline in PA was found after 26 weeks of treatment. This decline may be caused by the protocolized tapering of prednisolone, a medicine which may rapidly and strongly lower disease activity with a corresponding rapid improvement of physical functioning when given in a relative high dose at the start of treatment. In addition, protocolized intensification of treatment with etanercept was only possible from 26...
weeks. As a consequence, patients failing on previous protocolized treatment may have decreased PA in the period between week 13 and 26.

In general, this study shows a rapid increase of PA, which persists for at least one year. Regular PA has major health benefits for RA patients like increasing muscle strength and function, reducing risk on cardiovascular diseases and osteoporotic fractures, and improving psychological well-being.\textsuperscript{13}

Remarkably, our study population appears more physically active than the general Dutch population after one year of treatment, as only 66\% of an adult reference population met the PA guideline compared to 82\% in our study.\textsuperscript{14} Age- and sex-specific results show similar trends: our patients are more physically active compared to matched reference groups.\textsuperscript{14} This is most likely due to the tendency of trials to include healthier patients than the general patient population, even a pragmatic trial such as this one.

Other studies\textsuperscript{2,3,8,15} have shown either comparable or lower PA levels in RA patients than the general population, but these vary widely in disease activity, disease duration, age, sex, measurement tools and cut off values of (national) PA guidelines. Furthermore, some differences might be partly explained by cultural influences.

A limitation of our study might be the use of cut-off points to categorize levels of PA. We were aware that dichotomizing data results in loss of precision, but this method is a common way to report PA levels in guidelines and literature, rather than a sum of active minutes per week.

Other limitations of our study include the indirect measurement of PA through use of a questionnaire, with the risk of recall bias and socially desirable answers. The SQUASH has been described as a short and simple questionnaire.\textsuperscript{11} Still, our patients did not always fill out the questionnaire correctly and/or completely, which was reflected in missing, unrealistic or impossible answers (e.g. cycling 40 hours per day). In addition, some activities of the SQUASH domains overlap, in which case patients may fill out the same activity two or three times, overestimating PA. In our study 2\% of the SQUASH answers were manually adjusted, however, sensitivity analyses of our study showed no difference between crude and adjusted data.

The SQUASH has also been described as a fairly reliable and reasonably valid tool to assess habitual activity level.\textsuperscript{11} Still, eight patients (6\%) scored zero minutes PA at baseline. Although disease activity and pain will be high at the moment of diagnosis, it seems impossible that patients are completely inactive during one whole week. Therefore, we wonder if the questionnaire reflects the entire habitual PA pattern of daily activities. If not, PA may be systematically underestimated.

In conclusion, we demonstrated a longitudinal, inverse association between disease activity and PA in early RA patients treated in the COBRA-light trial. This study shows that our treat-to-target combination therapy is effective in decreasing disease activity and improves PA in early RA patients, a beneficial effect persisting for at least 1 year.
Author contributions
All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Ms Konijn had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design: Konijn, van Tuyl, den Uyl, ter Wee, Kerstens, Voskuyl, Nurmohamed, van Schaardenburg, Lems. Acquisition of data: Konijn, van Tuyl, den Uyl, ter Wee, Kerstens. Analysis and interpretation of data: Konijn, van Tuyl, Boers, Kerstens, Nurmohamed, Lems.

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

**TABLE 1.** Physical activity and DAS remission over time (n=140)

<table>
<thead>
<tr>
<th>DAS remission after 13 weeks</th>
<th>DAS remission after 26 weeks</th>
<th>DAS remission after 52 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>DAS ≥ 1.6</td>
<td>n=83 (59%)</td>
<td>DAS ≥ 1.6</td>
</tr>
<tr>
<td>DAS &lt; 1.6</td>
<td>n=57 (41%)</td>
<td>DAS &lt; 1.6</td>
</tr>
</tbody>
</table>

Patients meeting the WHO guideline for PA, n (%) 71 (86%) 55 (97%) * 58 (81%) 62 (91%) 66 (86%) 59 (94%)

Patients meeting the Dutch guideline for PA, n (%) 63 (76%) 51 (90%) * 51 (71%) 57 (84%) 57 (74%) 58 (92%) *

*Statistically significant different (p<0.05) compared to DAS ≥ 1.6 group (Chi square analyses); DAS = Disease Activity Score, PA = physical activity, WHO = World Health Organization.

**TABLE 2.** Physical activity and EULAR response over time (n=140)

<table>
<thead>
<tr>
<th>EULAR response after 13 weeks</th>
<th>EULAR response after 26 weeks</th>
<th>EULAR response after 52 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>None + moderate</td>
<td>Good</td>
<td>None + moderate</td>
</tr>
<tr>
<td>n=47 (34%)</td>
<td>n=93 (66%)</td>
<td>n=36 (26%)</td>
</tr>
</tbody>
</table>

Patients meeting the WHO guideline for PA, n (%) 37 (79%) 89 (96%)* 28 (78%) 92 (89%) 33 (79%) 92 (94%)*

Patients meeting the Dutch guideline for PA, n (%) 30 (64%) 84 (90%)* 24 (67%) 84 (81%) 28 (67%) 87 (89%)*

*Statistically significant different (p<0.05) compared to none + moderate responder group (Chi square analyses); DAS = Disease Activity Score, PA = physical activity, WHO = World Health Organization.

**TABLE 3.** Physical activity and ACR70 response over time (n=140)

<table>
<thead>
<tr>
<th>ACR70 response after 13 weeks</th>
<th>ACR70 response after 26 weeks</th>
<th>ACR70 response after 52 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>No response</td>
<td>ACR70 response</td>
<td>No response</td>
</tr>
<tr>
<td>n=92 (66%)</td>
<td>n=48 (34%)</td>
<td>n=76 (54%)</td>
</tr>
</tbody>
</table>

Patients meeting the WHO guideline for PA, n (%) 80 (87%) 46 (96%) 63 (83%) 57 (89%) 75 (84%) 50 (98%)*

Patients meeting the Dutch guideline for PA, n (%) 69 (75%) 45 (94%)* 53 (70%) 55 (86%)* 66 (74%) 49 (96%)*

*Statistically significant different (p<0.05) compared to no ACR70 response group (Chi square analyses); DAS = Disease Activity Score, PA = physical activity, WHO = World Health Organization.
References


