Improvements in Participation in Usual Daily Activities in Patients with Rheumatoid Arthritis Treated with Abatacept

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**ABSTRACT**

**Objective:** To examine changes in activity participation following abatacept treatment for rheumatoid arthritis (RA), and which factors contributed to such changes.

**Methods:** Data were analyzed from the Abatacept in Inadequate responders to Methotrexate (AIM) and Abatacept Trial in Treatment of Anti-TNF INadequate responders (ATTAIN) clinical trials of abatacept in patients with RA. Activity participation was evaluated by the validated Activity Participation Questionnaire (APaQ), along with measures of clinical response and health-related quality of life. Changes in the APaQ during the two study periods were compared between treatment groups. Multiple regression analyses were performed to investigate the determinants of change in activity participation. The relationship between clinical efficacy measures (including low disease activity state [LDAS], Disease Activity Score 28-defined remission, and European League Against Rheumatism [EULAR] responses) and changes in activity participation were investigated.

**Results:** Statistically significant, substantive improvements in activity participation were observed over the entire study period in patients treated with abatacept. Abatacept-treated patients showed improvements from baseline of 8.4 and 7.3 days in activity participation, compared with 4.5 and 1.4 days in the placebo group ($P < 0.005$ vs. placebo in both trials), at the end of AIM and ATTAIN, respectively. The Short Form-36 physical and mental component scores, patient global assessment, and the Health Assessment Questionnaire-Disability Index score were found to be the strongest determinants of changes in activity participation. Patients who achieved LDAS, disease remission and good EULAR responses experienced greater improvements in activity participation measures.

**Conclusions:** Abatacept treatment substantively and significantly improved patients’ ability to participate in their usual activities. The gain in activity was closely related to improvements in clinical status, physical function and quality of life.

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Introduction

The disabling course of rheumatoid arthritis (RA) severely impairs a patient’s physical function, and often results in reduced participation in social activities, including work and leisure [1,2]. This type of activity participation is central to a patient’s health-related quality of life (HRQoL) and sense of general well-being [3,4], and the inability to perform these activities can have a profound impact on a patient’s psychological and social health [4–6]. Capturing the patient’s perspective of how RA impacts their daily activities is not only critical to improving patient care, but it can also help inform other aspects of disease management, such as health policy and resource allocation [7]. Improvement in a patient’s physical functioning and subsequent return to normal activity is, therefore, an important treatment goal for RA.

There is a large body of evidence demonstrating that advances in RA therapy have brought tremendous improvements in terms of disease activity, physical function, and HRQoL. [8–13]. However, less is known about the extent to which these clinical benefits impact patients’ daily lives, and whether they translate into increased participation in daily and social activities. Evaluation of the impact of therapy on activity participation can provide valuable additional information to supplement the information gained from standard clinical and HRQoL assessments. This broader type of assessment to supplement the information gained from standard clinical and HRQoL assessments. This broader type of assessment of RA treatment is of increasing interest to researchers and in clinical practice [4,14], and is advocated by the conceptual model of the International Classification of Functioning, Disability and Health (ICF) for RA. The current ICF model for RA assessment consists of three components: functional impairment, activity limitation, and activity participation [15–17]. Although several measures are available to assess the impact of treatment on functional impairment and activity limitation, there has been a lack of direct measures that evaluate activity participation; as a result, this component has not yet been sufficiently examined. To address this, the Activity Participation Questionnaire (APaQ) was developed and validated [18]. The APaQ is a simple and direct measure consisting of two items that assess participation in usual daily activities, which is applicable regardless of age, gender, and work status, as well as all cultural and socioeconomic groups. Usual daily activities are defined as work, whether or not the work is paid, and any other activities the patient participates in during the day (e.g., household chores, personal care, etc.). The term ‘activity participation’ used in the APaQ refers to participation in usual daily activities.

The APaQ was developed under the guidance of practicing rheumatologists, with expertise in outcome measures, to be a simple and clinically relevant measure that could be easily administered in a clinical trial setting [18]. The resulting two items on the APaQ – activity limitation and activity participation – were derived from items on existing, validated questionnaires; the National Health Interview Survey Adult Core Questionnaire and the 36-item Short Form-36 (SF-36), respectively. During validation, both items of the questionnaire exhibited strong correlation with clinical improvements (American College of Rheumatology [ACR] and European League Against Rheumatism [EULAR] responses) and disease activity (minimal disease activity), and moderate correlations with patient-reported outcomes (Health Assessment Questionnaire-Disability Index [HAQ-DI], pain, fatigue, and patient global assessment), demonstrating construct validity. The APaQ also indicated reliability, internal consistency, and sensitivity to change [18].

Here we assess the effect of a biologic therapy, abatacept, on patients’ participation in usual daily activities, and examine which factors contribute most to changes in activity participation. Abatacept is a first-in-class, selective costimulation modulator that inhibits full T-cell activation, and it has previously demonstrated clinical efficacy in patients with RA and an inadequate response to methotrexate (MTX) [19,20] or anti-tumor necrosis factor (TNF) therapy [21]. Along with clinical efficacy measures and patient-reported outcomes, the APaQ [18] was assessed throughout the abatacept clinical trials, providing an opportunity to evaluate the effect of abatacept treatment on activity participation over time. Improvements in HRQoL with abatacept have been reported previously [12,13]; the aim of the current analysis is to determine whether abatacept treatment also leads to gains in patient activity participation.

Methods

Study designs and patient populations

Data used in this analysis were obtained from two randomized double-blind, placebo-controlled, multicenter, multinational, phase III clinical trials of abatacept in active RA patients: Abatacept in Inadequate responders to Methotrexate (AIM) [19] and Abatacept Trial in Treatment of Anti-TNF Inadequate responders (ATTAIN) [21]. The 12-month AIM study included 652 patients randomized 2:1 to receive abatacept or placebo on a background of MTX [19]. The 6-month ATTAIN study included 391 patients randomized 2:1 to receive abatacept or placebo on a background of disease-modifying anti-rheumatic drugs (DMARDs) [21]. Both studies were approved by ethical review boards, and written informed consent was obtained from the patients.

Outcomes assessment

In addition to the primary efficacy endpoints (ACR responses, HAQ-DI and radiographic progression for AIM; ACR responses and HAQ-DI for ATTAIN), multiple clinical and patient-reported outcomes were assessed in these studies.

Clinical outcomes

The Disease Activity Score 28 (DAS28) index combines tender and swollen joint counts, biomarker data, and patient’s global assessment of disease activity [22,23]. Scores of <3.2, 3.2 to ≤5.1, and >5.1 represent low, moderate, and high disease activity, respectively [24–26]. A change in DAS28 score of 1.2 (i.e., twice the measurement error) is considered to be clinically significant [27]. Patients are considered to be in remission if the DAS28 score is <2.6 [24].
The EULAR response criteria are based on the DAS28 and are a function of both current disease activity and the change in disease activity from baseline, with responses classified as good, moderate, or none [28]. A good response is defined as an improvement of >1.2 and a final score of <3.2; a moderate response is indicated by an improvement of >1.2 and a final score of ≥3.2, or an improvement of 0.6 to 1.2 and a final score of ≤5.1; and a patient with any other combination of DAS28 improvement and final score is classified as a non-responder.

**Patient-reported outcomes**

Physical function was measured by the HAQ-DI, which assesses patients’ ability to complete eight categories of activities of daily living [29]. Within each category, patients report the degree of difficulty they have experienced over the past 7 days when performing these activities (none, some difficulty, much difficulty, unable to do). An aggregate score that adjusts for the use of aids and devices is computed on a scale of 0 to 3, with 0 representing no disability and 3 indicating complete disability.

Quality of life was assessed by SF-36 score, which includes eight domain scores, including physical functioning, role limitation due to physical problems, bodily pain, general health perception, vitality, social functioning, role limitation due to emotional problems, and mental health; all domains were evaluated over the previous 4 weeks [30]. The scores range from 0 to 100, with higher scores indicating better quality of life. The scores were normalized to a mean of 50 and standard deviation of 10 using population norms. Two summary scores were produced from the eight domains – the physical component summary (PCS) and the mental component summary (MCS).

Fatigue severity was measured on a 0 to 100 mm visual analog scale, with higher scores indicating greater fatigue [31]. Sleep quality was assessed by the sleep problems index from the Medical Outcomes Study Sleep Module (MOS-Sleep) [32]. The sleep problems index ranges from 0 to 100, with higher scores indicating more problems with sleep and worse sleep quality.

**Activity participation**

The APaQ is a validated instrument consisting of two items that measure the degree to which patients are limited in participating in usual daily activities due to RA over the past 30 days [18]. The ‘usual daily activities’ (as determined by the patient), can include paid/non-paid work, household chores, taking care of children, volunteering, and any other activities that the patient usually does. Two questions measure two different aspects of participation, with the first question focusing on absenteeism and the second question on presenteeism. The first asks “during the past 30 days, on about how many days did your RA keep you from doing your usual activities?” The response is a number of days between 0 and 30. The second question asks ‘during the past 30 days, how often were you able to perform your usual activities completely, in spite of your RA?’ The responses are listed as six categories, and converted into an ‘activity completion’ score ranging from 1 to 6 (1=all of the time, 2=most of the time, 3=a good bit of the time, 4=some of the time, 5=a little of the time, and 6=none of the time). Higher scores on both items represent less activity participation. The APaQ was administered monthly in both the AIM and ATTAIN trials.

**Statistical analysis**

Three types of analyses were performed on the activity participation data from AIM and ATTAIN. First, mean change over time in the APaQ items were compared between treatment groups using analysis of covariance, adjusting for baseline values. Second, a risk-adjusted predictive regression model was performed to investigate the determinants of change in activity participation. Two separate models were constructed, one with the change from baseline in days of limited activity (first item of the APaQ; Model 1) as the dependent variable, the other used the change from baseline in activity completion score (second item of the APaQ; Model 2) as the dependent variable. Both models included change from baseline in HAQ-DI score, SF-36 scores, patient and physician global assessments, sleep problems index, pain, fatigue, tender joint count, and swollen joint count as the independent variables. Both regression models adjusted for confounding variables, such as age, sex, race, duration of RA, and baseline APaQ scores. A tolerance below 0.20 was used as an indicator of a problem with multicollinearity for each model [33]. Third, to examine the relationship between changes in disease status and changes in activity participation, the changes in APaQ were analyzed according to clinical responses as assessed by variants of DAS28, including Low Disease Activity State (LDAS; DAS28 ≤ 3.2), DAS28 remission (DAS28 < 2.6), and EULAR response categories. All calculations were based on an intent-to-treat population, defined as all randomized patients with post-baseline assessments who received at least one dose of study medication. Missing values, including those for patients who discontinued, were imputed using the last observation carried forward method. Drop-out rates from the AIM and ATTAIN trials were 16.1% and 17.6%, respectively, for all treated patients. Values were missing for the APaQ for 2.5% and 3.9% of patients in the AIM and ATTAIN trials, respectively. Analyses were performed using SAS version 9.1 (SAS Institute Inc., Cary, NC, USA).

**Results**

**Patient baseline characteristics**

At baseline, patient characteristics in the abatacept and placebo groups were similar in both AIM and ATTAIN studies (Table 1). Patients had moderate-to-severe RA, with mean HAQ-DI scores ranging from 1.7 to 1.8, mean DAS28 scores of 6.4 to 6.5, and PCS and MCS scores that were considerably below the population norm of 50.

**Activity participation**

Substantial limitation in activity participation was noted at baseline. Patients reported a mean of 14 to 17 days of limited
participation in usual activities over the past 30 days (i.e., approximately half a month), and a mean APaQ activity completion score of 3.6 to 3.8, which indicated that, on average, patients had been able to complete their usual activities between ‘a good bit of the time’ and ‘some of the time’.

In AIM, the gains in days of activity participation between patients on abatacept and placebo started to separate from Month 1 after treatment, and the differences were significant from Month 2 ($P < 0.005$) onward (Fig. 1A). The difference between abatacept and placebo (7.97–8.95 days vs. 4.58–5.52 days) stabilized at Month 4 and was maintained through 12 months. Patients in the ATTAIN trial experienced similar improvements (Fig. 1B). Mean improvements for the abatacept group (6.11–7.80 days throughout the study period) were at least three times greater than the changes in the placebo group (1.68–2.30 days). Changes over time in the activity completion scores followed the same pattern, with the improvements seen with abatacept significantly greater than those seen with placebo ($P < 0.005$ from Month 3 onwards in both studies; Figs. 1C and 1D).

To examine the actual number of days per month that patients were active (able to participate in their usual activities), the mean improvements in days of limited activity at Month 6 (in AIM and ATTAIN) and Month 12 (in AIM) were compared (Fig. 2). In the AIM study, patients in the abatacept group reported ability to participate in usual activities on only 16.3 of 30 days at baseline (Fig. 2A). After 6 months of treatment, patients were able to participate in daily activities on 24 days per month. This represented a gain of 7.7 activity days (47.2%) from baseline, compared with an increase of 3.9 days (23.5%) in the placebo group ($P < 0.0001$). At Month 12, abatacept-treated patients had gained another 0.7 activity days (24.7 days in usual activity participation, a 51.5% increase in active days from baseline) when compared with 0.6 days gained in the placebo group (21.1 days in usual activity participation, a 27.1% increase in active days from baseline; $P < 0.0001$ for abatacept versus placebo). In the ATTAIN study, patients had even fewer active days at the beginning of the study (12.7 days in the abatacept group, 14.1 days in the placebo group; Fig. 2B). After 6 months of treatment, patients in the abatacept group gained 7.3 days (20.0 days in usual activity participation, a 51.5% increase in active days from baseline) compared with 1.4 days gained in the placebo group (15.5 days in usual activity participation, a 9.9% increase in active days from baseline; $P = 0.0002$ for abatacept versus placebo).

Over the 12-month AIM study, abatacept-treated patients gained a cumulative 100.1 days of activity participation compared with the cumulative gains of 58.2 days in the placebo group. Therefore, patients treated with abatacept nearly doubled the gains in active days during the 12-month study period. Similarly, in the 6-month ATTAIN study the patients treated with abatacept gained a cumulative 38.1 days compared with 12.8 days for patients treated with placebo.

### Determinants of activity participation

From the regression analysis, the major contributors for changes in days of limited activity (Model 1) were the PCS and MCS of the SF-36, and patient global assessment (Table 2). They explained over 30% of the variance in the activity data. The PCS and MCS were the variables most highly predictive of changes in days of limited activity ($P < 0.0001$), with parameter estimates of −0.32 and −0.16, respectively. Thus, a 1-unit increase (improvement) in SF-36 PCS was associated with a re-

<table>
<thead>
<tr>
<th>Table 1 - Baseline characteristics.</th>
<th>AIM (MTX-inadequate responders)</th>
<th>ATTAIN (anti-TNF-inadequate responders)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Abatacept ~10 mg/kg* (n=433)</td>
<td>Placebo (n=219)</td>
</tr>
<tr>
<td>Age in years</td>
<td>51.5 ± 12.9</td>
<td>50.4 ± 12.4</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>337 (78)</td>
<td>179 (82)</td>
</tr>
<tr>
<td>Caucasian, n (%)</td>
<td>379 (88)</td>
<td>193 (88)</td>
</tr>
<tr>
<td>Duration of RA, years</td>
<td>8.5 ± 7.3</td>
<td>8.9 ± 7.1</td>
</tr>
<tr>
<td>HAQ-DI score (0–3)</td>
<td>1.7 ± 0.7</td>
<td>1.7 ± 0.6</td>
</tr>
<tr>
<td>Patient global assessment of</td>
<td></td>
<td></td>
</tr>
<tr>
<td>disease activity (0–100)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain (0–100)</td>
<td>63 ± 21</td>
<td>63 ± 21</td>
</tr>
<tr>
<td>Fatigue (0–100)</td>
<td>63 ± 23</td>
<td>66 ± 23</td>
</tr>
<tr>
<td>APaQ</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Days of limited activity (0–30)</td>
<td>14.2 ± 11</td>
<td>14.4 ± 12</td>
</tr>
<tr>
<td>Activity completion score (1–6)</td>
<td>3.6 ± 1.4</td>
<td>3.6 ± 1.4</td>
</tr>
<tr>
<td>SF-36 score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical component</td>
<td>30.6 ± 7.3</td>
<td>30.7 ± 7.5</td>
</tr>
<tr>
<td>Mental component</td>
<td>41.8 ± 11.4</td>
<td>40.8 ± 11.2</td>
</tr>
<tr>
<td>DAS28</td>
<td>6.4 ± 0.08</td>
<td>6.4 ± 0.11</td>
</tr>
</tbody>
</table>

Note: Values in the table other than n (%) are mean (± standard deviation). AIM, Abatacept in inadequate responders to Methotrexate; APaQ, Activity Participation Questionnaire; ATTAIN, Abatacept Trial in Treatment of Anti-TNF Inadequate responders; DAS28, Disease Activity Score 28; HAQ-DI, Health Assessment Questionnaire Disability Index; MTX, methotrexate; TNF, tumor necrosis factor; RA, rheumatoid arthritis; SF-36, Short Form-36.

* Fixed-dose abatacept, ~10 mg/kg according to weight range (<60, 60–100, or >100 kg received 500, 750 or 1000 mg, respectively).
duction of 0.32 days of limited activity and, therefore, a gain in days of activity participation. Parameter estimates are negative for SF-36 score correlations because improvements in these scores go in the opposite direction to improvements in the APaQ (i.e., reductions in SF-36 represent improvements, and reductions in APaQ scores represent worsening). For all other outcomes assessed, parameter estimates are positive because improvements run in the same direction (i.e., reductions in scores represent improvements). Fatigue, HAQ-DI score, and tender joint count also contributed to changes in days of limited activity. Key contributors to changes in activity completion (Model 2) were the HAQ-DI, PCS, and MCS because they explained 26% of the variance. The strongest predictor of change in activity completion was the HAQ-DI score (parameter estimate 0.281; \( P < 0.0001 \)). Thus, a 1-unit decrease (improvement) in HAQ-DI was associated with a decrease (improvement) of 0.28 units in the activity completion score.

Other important contributors of change in activity completion were sleep and patient global assessment. For both models, tolerances ranged from 0.4 to 0.74, indicating that multicollinearity was not an issue.

Changes in activity participation according to clinical responses

Improvements in activity participation were consistent with changes in disease activity (Table 3). In patients achieving LDAS (DAS28 < 3.2), gains in days of activity participation and activity completion scores were about twice those for patients who did not have LDAS at study endpoint. These differences were equally pronounced when patients in remission (DAS28 < 2.6) were compared with those who were not. Similarly, when the results were stratified by EULAR response, patients with a good response progressed better than those with a
moderate or non-response. In the AIM study, patients achieving a good EULAR response improved 11.3 days of limited activity, compared with gains of 7.85 and 0.25 days in moderate and non-responders, respectively. Patients who achieved a good EULAR response also improved by 1.96 points on the activity completion scores compared with improvements of 0.95 and 0.11 points in moderate and non-responders, respectively. Similar results were observed in the ATTAIN study (Table 3).

**Discussion**

In this study we examined the changes in daily activity participation and the factors that contribute to such changes using data from the AIM and ATTAIN trials of abatacept in patients with RA. Abatacept substantively and significantly improved patients’ ability to participate in their usual daily activities, whether these activities were or were not work related. Improvements in activity participation were consistent with improvements in clinical responses (LDAS, DAS28-defined remission, and EULAR responses). Changes in both physical and mental aspects of quality of life were strong contributors to changes in patients’ activity participation.

Patients reported substantial limitations in activity participation at baseline. Abatacept-treated patients demonstrated meaningful improvements in the number of activity participation days by Months 6 and 12, with gains of around 50% over 6 months in the AIM trial. There were continued gains in activity completion scores from Months 6 to 12 for abatacept-treated patients in the AIM trial, demonstrating that initial improvements in productivity were maintained.

Over 6 and 12 months, abatacept-treated patients reported greater reductions in days of limited activity, and, therefore, greater improvements in days of activity participation, compared with placebo-treated patients. Significant improvements were observed as early as Month 2, and the treatment difference was maintained through 12 months in AIM and through 6 months in ATTAIN. Considering the cumulative number of activity days gained during the study periods, the difference between the abatacept and placebo groups was especially prominent. Importantly, reductions in days of limited activity for abatacept-treated patients were greater than the minimal clinically important difference (MCID) [34] of 4 days per month, from at least Day 57 in both AIM and ATTAIN. The substantial and clinically meaningful improvements seen in activity participation, which would have an important effect...
on patients’ work and social lives, clearly demonstrate the real-life impact of an effective treatment strategy over time, when compared with a sub-optimal regimen.

It was demonstrated that patients who experienced clinically meaningful improvements in clinical response (LDAS, DAS28-defined remission, and EULAR good or moderate response) also demonstrated greater improvements in activity participation, as assessed by the APaQ. Benefits to activity participation may be of equal, if not greater, importance to patients than improvements in clinical outcomes. Characterizing this relationship helps to interpret the real-life relevance of clinical responses, confirming that improvements in clinical outcomes are complemented by improvements in participation in daily activities. Furthermore, the magnitude of improvement in each APaQ item score correlated with the magnitude of improvement in clinical response, with days of limited activity and activity completion.

### Table 2 – Determinants of change in activity participation: clinical and patient-reported outcomes.

<table>
<thead>
<tr>
<th>Change from baseline</th>
<th>Parameter estimate (SE)</th>
<th>Partial R²</th>
<th>P value partial F-test</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Model 1: Change in days of limited activity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SF-36 physical component score</td>
<td>−0.32 (0.05)</td>
<td>0.2203</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>SF-36 mental component score</td>
<td>−0.16 (0.03)</td>
<td>0.0681</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Patient global assessment</td>
<td>0.04 (0.02)</td>
<td>0.0203</td>
<td>0.0103</td>
</tr>
<tr>
<td>Fatigue</td>
<td>0.04 (0.02)</td>
<td>0.0044</td>
<td>0.0216</td>
</tr>
<tr>
<td>HAQ-DI</td>
<td>1.66 (0.75)</td>
<td>0.0039</td>
<td>0.0286</td>
</tr>
<tr>
<td>Tender joint count</td>
<td>0.05 (0.02)</td>
<td>0.0023</td>
<td>0.0694</td>
</tr>
<tr>
<td>Intercept</td>
<td>0.19 (0.47)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td><strong>Model 2: Change in activity completion score</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HAQ-DI</td>
<td>0.281 (0.119)</td>
<td>0.1817</td>
<td>0.0181</td>
</tr>
<tr>
<td>SF-36 physical component score</td>
<td>−0.051 (0.007)</td>
<td>0.0346</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>SF-36 mental component score</td>
<td>−0.028 (0.005)</td>
<td>0.0406</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Sleep index</td>
<td>0.008 (0.003)</td>
<td>0.0045</td>
<td>0.0173</td>
</tr>
<tr>
<td>Patient global assessment</td>
<td>0.004 (0.002)</td>
<td>0.0019</td>
<td>0.1186</td>
</tr>
<tr>
<td>Intercept</td>
<td>−0.039 (0.066)</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

Note: Multiple regression analysis (R² = 0.3193, P value F-test <0.0001). Both independent (those listed in the table) and dependent (days of limited activity [range of 0–30] and activity completion [range of 1–6]) variables were expressed as a change from baseline. Multiple regression models were adjusted for age, sex, race, duration of RA, all outcomes variables. Note that parameter estimates are negative for SF-36 scores correlations because improvements in these scores go in the opposite direction to improvements in the APaQ (i.e., reductions in SF-36 represent worsening), for all other outcomes assessed, parameter estimates are positive because improvements run in the same direction (i.e., reductions in scores represent improvements). APaQ, Activity Participation Questionnaire; HAQ-DI, Health Assessment Questionnaire-Disability Index; RA, rheumatoid arthritis; SE, standard error; SF-36, Short Form-36.

### Table 3 – Improvements in activity participation according to clinical response at study endpoint.

<table>
<thead>
<tr>
<th></th>
<th>LDAS*</th>
<th>DAS28-defined remission†</th>
<th>EULAR response</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>AIM</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change in days of limited activity (0–30)</td>
<td>n=122</td>
<td>n=482</td>
<td>n=76</td>
</tr>
<tr>
<td>Change in activity completion score (1–6)</td>
<td>11.10 (11.02)</td>
<td>6.07 (11.42)</td>
<td>11.09 (11.01)</td>
</tr>
<tr>
<td><strong>ATTAIN</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change in days of limited activity (0–30)</td>
<td>n=37</td>
<td>n=275</td>
<td>n=21</td>
</tr>
<tr>
<td>Change in activity completion score (1–6)</td>
<td>8.31 (10.38)</td>
<td>4.38 (11.94)</td>
<td>10.40 (12.34)</td>
</tr>
</tbody>
</table>

Note: Data are mean (standard error); days of limited activity is expressed as the number of days (0–30) on which the patient participated in usual activities. Activity completion is expressed as a score ranging from 1–6. Study endpoint is Month 12 for AIM, and Month 6 for ATTAIN. The positive values indicate improvement (reduction) in days of limited activities and activity completion score. The T-test was used to determine the statistical significance of the improvement in APaQ items and LDAS or DAS28 remission (P < 0.05 for all pairwise comparisons). The F-test was used to determine the statistical significance of the improvement in APaQ items and the EULAR responses (P < 0.001 for all pairwise comparisons).

AIM, Abatacept in Inadequate responders to Methotrexate; APaQ, Activity Participation Questionnaire; ATTAIN, Abatacept Trial in Treatment of Anti-TNF Inadequate responders; DAS28, Disease Activity Score 28; EULAR, European League Against Rheumatism; LDAS, Low Disease Activity State.

* LDAS is defined as DAS28 ≤3.2; † DAS28-defined remission is a DAS28 of <2.6.
activity participation increasing incrementally with the proportion of patients with LDAS, DAS28-defined remission, and moderate and good EULAR responses. The association between APaQ scores and these commonly used, validated measures of clinical benefit provide evidence for the clinical relevance of this measure.

Given that improved activity participation is so valuable to patients, it is important to understand which factors contribute to changes in days of activity. Using a regression analysis technique we assessed the impact of a variety of clinical measures on both items of the APaQ to evaluate this. Changes in SF-36 physical and mental component measures were important determinants of change in both items of the APaQ, even after the adjustment of confounders and input variables. There was some small variation in the findings between the two models, with PCS and MCS scores being the most important determinants of change in activity limitation, and HAQ-DI the most important determinant of change for activity participation, although all of these outcomes influenced both scores. Given that the two items are quite distinct concepts in their own right (i.e., days of limitation relates to absenteeism, while activity participation reflects presenteeism), it is expected that slightly different factors would contribute to the changes of these variables. In this case, both the physical and mental aspects are highly predictive of a patient being unable to perform an activity. Once the patient is able to participate, physical function (HAQ-DI) is more predictive of restrictions to conducting the activity. Taking this into consideration, the small variation between these items is not entirely surprising. The effects from the mental and physical components were comparable in strength. These observations are consistent with previously published findings, which suggest that RA not only affects patients’ physical health, but also has a tremendous effect on mental health [12]. Previous reports on clinical trials with abatacept have demonstrated that treatment with abatacept improved both physical and mental health [12,13]. These findings further support the notion that physicians need to look beyond traditional measures of clinical assessments, and try to understand the impact of treatment on overall quality of life, including both physical and mental aspects.

Participation in daily and social activities is a pivotal contributor to general health and well-being; improving levels of participation – and, thus, involvement in society – is of high importance to patients with RA [4]. The ICF emphasizes that functional impairment, activity limitation, and activity participation should all be evaluated as part of a multidisciplinary assessment of health in patients with RA. Although some of the SF-36 domains address the levels of difficulties of activity participation (e.g., the role physical and the role emotional and social functioning), the APaQ provides direct assessment on the number of active days, which is more readily interpretable from clinical and societal perspectives. Furthermore, because multiple factors affect activity participation, the APaQ covers a broader scope than the particular SF-36 physical domains and can be used as a measure to supplement the SF-36 to provide additional insights into the impact of an intervention on a patient’s real life.

The APaQ provides a real-life disease parameter that describes and quantifies the effect of treatment on days of activity participation. This simple approach allows patients and physicians the opportunity to evaluate the direct impact that effective treatment has on actual days of activity, allowing increased participation in social roles, and takes the role of patient-reported outcomes a step further towards addressing the impact of treatment on patients’ personal lives. These findings support the current ICF framework, which encourages the health-care profession to look beyond traditional clinical variables to other aspects of a patient’s life.

For this evaluation a global assessment of activity participation was performed, unlike previous studies that mainly focused on one specific area of activity, namely employment or the ability to work [35–37]. In order to provide a complete profile of how a patient responds to treatment, measuring work alone is obviously not sufficient. Work is not applicable to all patients with RA, as according to prior research only 37% to 43% of patients with RA less than 65 years old are employed [38]. Hence, changes in work activity presented in clinical trials would not necessarily represent the entire population, and may only describe a subset of patients in the study. In addition, it should be recognized that patients who do not work may experience improvements in non-work related activities, and that work only reflects activities during 20 to 21 working days/month and for 8 hours/day. Thus, measuring work performance alone provides an incomplete picture of the impact of treatment on the majority of activities of daily living, and although employment and productivity are important to society and should be assessed where possible, clinicians should look beyond work productivity and examine every day real-life activity.

Further to this, the effect of disability on individual measures of activity participation may vary according to the value that individuals place on affected activities [39]. Non-work activities, such as social activities, parenting, family activities, and volunteering can be equally important to some patients; for example, some patients may give up activities such as work in order to have the time, energy, or resources to perform a parenting role. Alternatively, some patients will view employment as most important, and they may forgo other activities in order to fulfill work commitments. This further supports the concept that measuring any one specific area of activity is insufficient, and that a broader measure, such as the APaQ, would provide a more comprehensive picture of the impact of treatment on activity.

In this study, improvements in activity participation were also observed in patients who received placebo, although notably less so than those observed in abatacept-treated patients. This may be attributed to the placebo effect often experienced in the clinical trial setting, which results from the special care and attention patients may receive in this environment. In addition, patients in the AIM and ATTAIN trials were receiving background MTX or other DMARD therapy, which may also account for some treatment effect. Importantly, significant differences between the two treatment groups were reported in both the AIM and ATTAIN studies, which can be attributed to treatment with abatacept.

We acknowledge there are several potential limitations of the present study. In evaluating the contribution of clinical
outcome measures to changes in activity participation, there may be unknown confounders or data that are not available for incorporation, such as socioeconomic and employment status. Nevertheless, after adjusting for age, sex, race, and duration of RA, it was found that improvements in both items of the APaQ were highly correlated with improvements in the physical and mental components of SF-36. In addition, this analysis was based on data from clinical trials, which, given the strict enrollment criteria employed, may not be entirely representative of patients seen in clinical practice. Therefore, caution should be used when drawing conclusions with respect to a wider RA patient population, and future research is needed to examine usual daily activity participation in a heterogeneous population. Finally, while an MCID has been validated for the number of days of activity limitation, no such threshold has been established for activity completion scores and, therefore, it is not certain if improvements in this item reflect clinically meaningful changes for the patient. A validation study to establish the MCID in improvement in activity completion scores is required to confirm whether these changes are clinically meaningful.

Conclusions

In conclusion, patients with RA experience substantial restrictions in participating in daily activities, including both work and non-work activities. Abatacept significantly improved patients’ ability to participate in usual daily activities, as assessed by the APaQ, over 12 and 6 months of treatment in the AIM and ATTAIN trials, respectively. Improvements in both physical and mental health were found to be the most important contributors to changes in activity participation. Changes in activity participation were clinically meaningful and were closely related to improvements in clinical outcomes, physical function, and HRQoL. These data support the broader evaluation of activity participation in the assessment of treatment for RA, in alignment with the ICF model for RA assessment.

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