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ORIGINAL ARTICLE

Effects of Achieving Target Measures in Rheumatoid Arthritis on Functional Status, Quality of Life, and Resource Utilization: Analysis of Clinical Practice Data

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Objective. **To evaluate associations between achieving guideline-recommended targets of disease activity, defined by the Disease Activity Score in 28 joints using C-reactive protein level (DAS28-CRP) <2.6, the Simplified Disease Activity Index (SDAI) ≤3.3, or the Clinical Disease Activity Index (CDAI) ≤2.8, and other health outcomes in a longitudinal observational study.**

Methods. **Other defined thresholds included low disease activity (LDA), moderate (MDA), or severe disease activity (SDA). To control for intraclass correlation and estimate effects of independent variables on outcomes of the modified Health Assessment Questionnaire (M-HAQ), the EuroQol 5-domain (EQ-5D; a quality-of-life measure), hospitalization, and durable medical equipment (DME) use, we employed mixed models for continuous outcomes and generalized estimating equations for binary outcomes.**

Results. **Among 1,297 subjects, achievement (versus nonachievement) of recommended disease targets was associated with enhanced physical functioning and lower health resource utilization. After controlling for baseline covariates, achievement of disease targets (versus LDA) was associated with significantly enhanced physical functioning based on SDAI ≤3.3 (ΔM-HAQ −0.047; $P = 0.0100$) and CDAI ≤2.8 (−0.073; $P = 0.0003$) but not DAS28-CRP <2.6 (−0.022; $P = 0.1735$). Target attainment was associated with significantly improved EQ-5D (0.022–0.096; $P < 0.0030$ versus LDA, MDA, or SDA). Patients achieving guideline-recommended disease targets were 36–45% less likely to be hospitalized ($P < 0.0500$) and 23–45% less likely to utilize DME ($P < 0.0100$).**

Conclusion. **Attaining recommended target disease-activity measures was associated with enhanced physical functioning and health-related quality of life. Some health outcomes were similar in subjects attaining guideline targets versus LDA. Achieving LDA is a worthy clinical objective in some patients.**

INTRODUCTION

Rheumatoid arthritis (RA) affects 0.5–1.0% of adults in industrialized societies (1). This chronic, systemic inflammatory disorder causes erosive damage to articular cartilage and subchondral bone, with joint swelling, deformity, pain, stiffness, and fatigue. Many patients with RA experience diminished health-related quality of life (HRQOL) as

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Significance & Innovations

- Data are limited on the benefits of achieving guideline-recommended targets, as well as other measures of disease activity, on the outcomes of physical functioning, quality of life, and health care resource utilization in established rheumatoid arthritis (RA) within "real-world" clinical practice settings.
- Our study evaluated associations between achievement of guideline targets, low disease activity (LDA), moderate disease activity (MDA), or severe disease activity (SDA) and physical functioning, quality of life, and health care resource utilization.
- In our observational study of a mainly established RA population, patients who achieved (versus did not achieve) targets had improved physical functioning and quality of life, as well as lower health care resource utilization. However, benefits of attaining target versus LDA were not uniform across all definitions of disease activity; for example, patients achieving Simplified Disease Activity Index and Clinical Disease Activity Index (but not Disease Activity Score in 28 joints using C-reactive protein level) targets had significantly better physical functioning.
- We observed that, with each increasing (worsening) measure of disease activity (i.e., LDA, MDA, SDA), subjects experienced decreased physical functioning and health-related quality of life, as well as increased resource use. Hence, LDA may also be a clinically worthwhile alternative in patients who do not achieve remission.

well as increased disability and comorbidities. Because of related disability, reduced worker productivity, expensive therapy with biologic drugs, institutionalization, joint replacement surgery, and increased use of durable medical equipment (DME), RA is a costly condition, accounting for annual health care expenditures of approximately $128 billion in the US (2–4).

Although there is no cure for RA, treatment with disease-modifying antirheumatic drugs (DMARDs) and biologic DMARDs (bioDMARDs) has improved health outcomes for RA patients. Increasingly, treatments oriented toward prespecified disease targets are emerging as the prevailing RA management paradigm. This treat-to-target approach involves aiming for a prespecified target of disease activity, frequently monitoring disease levels, and titrating medication regimens to goals (where therapies are acceptably tolerated). Such strategies have proved to be more effective than routine care, with randomized controlled trials (RCTs) and other studies supporting their value in attenuating RA signs and symptoms, ameliorating functional status, and mitigating or halting radiographic progression (5–8).

The most desirable target measure of disease activity is remission, which signifies a condition of negligible or no inflammatory activity, total arrest of structural joint damage, and the optimum achievable reversal of disability (6,9–11). In previous consensus guidelines, remission was operationally defined as a Disease Activity Score in 28 joints using C-reactive protein level (DAS28-CRP) of <2.6 (12). However, some patients with DAS28-CRP <2.6 experience residual disease activity, including inflammation, pain, and joint tenderness and swelling in ankle and foot joints (5,13–18). Although DAS28-CRP <2.6 no longer constitutes remission, it remains a valid treatment target.

In more recent times, more stringent consensus definitions of remission have been developed that are both index based (Simplified Disease Activity Index [SDAI] score ≤ 3.3 [3,13,19]) and Boolean based. The Boolean-based definition (13) requires a score of ≤ 1 on each of the following items: tender joint count in 28 joints, swollen joint count in 28 joints, CRP level (in mg/dl), and patient global assessment (on a 0–10-cm visual analog scale [13,19]).

Clinical studies have increasingly included different target measures of disease activity as primary efficacy end points (20–23). Because such trials typically include "selected" patient populations with high adherence, severe RA activity, and short study durations, their findings may be less generalizable to clinical practice compared with data from observational studies (7,24–29).

Limited empirical evidence is available concerning patients with established RA in routine clinical practice to support the benefits of achieving different definitions of target measures of disease activity in relation to functional status, HRQOL, and health care resource utilization. To our knowledge, no observational study has assessed the potential clinical implications of achieving each of these different disease cut points across various efficacy and resource use outcome measures.

To close this gap in knowledge, we sought to evaluate associations between achieving different definitions of target measures of disease activity and the following health outcomes in a longitudinal observational study of a clinically representative RA patient cohort: 1) physical functioning (daily activities) according to the modified Health Assessment Questionnaire (M-HAQ), 2) HRQOL according to the EuroQol 5-domain (EQ-5D) measure, and 3) health care resource utilization according to hospitalizations and DME use.

PATIENTS AND METHODS

We utilized data from the Brigham and Women's Hospital Rheumatoid Arthritis Sequential Study (BRASS; ClinicalTrials.gov identifier NCT01793103), which was initiated in 2003–2004. Details concerning the study design have been reported elsewhere ([30–32]; for further details, see http://www.brassstudy.org.). The BRASS Registry is a single-center, prospective, observational longitudinal cohort of $>1,200$ adults with established or recent-onset RA who are being followed by a hospital-based practice of 21 rheumatologists in Boston. Physicians assessed patient demographic and clinical characteristics, disease activity, and laboratory parameters at baseline and annually thereafter. Followup postal questionnaires to assess patient-reported outcomes were also mailed to patients every 6 months. In the BRASS Registry, disease activity was evaluated during each annual rheumatology visit. However, because visits seldom occurred exactly at

12 months, for this analysis windows of 6 months (±3 months) around the 12-month physician visits were created to evaluate annual disease activity. In addition, windows of 3 months (±1.5 months) were created around the 6-month patient survey. Therefore, the followup time was divided into distinct intervals as follows: time interval 1 extended from 5 to 8 months (midpoint = 6 months); interval 2 extended from 9 to 15 months (midpoint = 12 months); interval 3 extended from 16 to 20 months (midpoint = 18 months); interval 4 extended from 21 to 27 months (midpoint = 24 months), and so on, extending up to 5 years.

Measures of disease activity assessed annually by physicians included the DAS28-CRP, the SDAI, and the Clinical Disease Activity Index (CDAI). Three different desired target measures of disease activity were considered in the current analysis: DAS28-CRP <2.6, SDAI ≤ 3.3, and CDAI ≤ 2.8 (33–35). These disease targets were categorized as having been met or not met as follows: DAS28-CRP <2.6 versus ≥ 2.6, SDAI ≤ 3.3 versus >3.3, and CDAI ≤ 2.8 versus >2.8.

In addition to categorizing and comparing disease activity in a binary manner, we compared achievement of the target measures to attainment of multiple other cut points. Achievement of DAS28-CRP <2.6 was compared to attainment of low disease activity (LDA; $2.6 <$ DAS28-CRP ≤ 3.2), moderate disease activity (MDA; $3.2 <$ DAS28-CRP ≤ 5.1), or severe disease activity (SDA; DAS28-CRP >5.1) (33,35). Similarly, achievement of SDAI ≤ 3.3 was compared to attainment of LDA ($3.3 <$ SDAI ≤ 11.0), MDA ($11.0 <$ SDAI ≤ 26), or SDA (SDAI >26) (36,37). Finally, achievement of CDAI ≤ 2.8 was compared to attainment of LDA ($2.8 <$ CDAI ≤ 10.0), MDA ($10.0 <$ CDAI ≤ 22.0), or SDA (CDAI >22.0) (34).

The patient-reported outcomes of physical functioning as measured by the M-HAQ, HRQOL as measured by the EQ-5D using US population-based preference weights (36), and health care resource utilization as measured by whether patients did (or did not) use DME or were (or were not) hospitalized, were captured during the 6-month postal survey. The patient-reported outcome measures incorporated within the BRASS case report forms were validated questionnaires that have been widely used in other RA registries as well as clinical trial settings (33–35,37). DME included walkers, wheelchairs, standers, and patient lifts.

Ethics. The BRASS Registry has been conducted in accordance with International Society for Pharmacoepidemiology Guidelines for Good Pharmacoepidemiology Practices, applicable regulatory requirements, and ethical tenets originating in the Declaration of Helsinki. The study protocol and informed consent document were reviewed and approved by the Brigham and Women's Hospital Institutional Review Board. All patients provided written informed consent before participating in the BRASS Registry. Anonymous (de-identified) patient data in the present study were compliant with the Health Insurance Portability and Accountability Act. Maintenance of patient confidentiality was assured by assigning each subject a randomized identification number upon enrollment in the BRASS Registry.

Statistical analyses. Baseline characteristics were expressed as means ± SDs and numbers (%). Univariate and multivariate analyses were conducted to evaluate associations between achievement of prespecified, guideline-recommended target measures of disease activity (independent variables of interest) and the outcome measures of M-HAQ (continuous variable), EQ-5D (continuous variable), DME use (categorical variable), and all-cause hospitalization (categorical variable; dependent variables).

Univariate analyses involved comparisons of mean scores on the M-HAQ and EQ-5D, in patients who either did or did not achieve the above definitions of targets for the DAS28-CRP, SDAI, and CDAI, using Student's *t*-test and analysis of variance for comparing these measures in individuals attaining target, LDA, MDA, or SDA. Similarly, proportions of patients using DME or being hospitalized were compared in patients who either did or did not achieve the above definitions of targets, using the chi-square test and visual inspection comparisons between individuals attaining guideline-recommended targets, LDA, MDA, or SDA.

To control for intraclass correlation of the panel data in BRASS, we used mixed models with Toeplitz covariance structure to estimate both the effects of the achievement of target measures or other levels of disease activity on the dependent variables, i.e., the primary outcome measure of physical functioning assessed by the M-HAQ and the secondary outcome measure of HRQOL assessed by the EQ-5D. Generalized estimating equations with binomial distribution and logit link function were utilized for binary outcomes such as DME use and all-cause hospitalization. Baseline covariates included in these models were sociodemographic, laboratory measures, subjective (patient-reported), and physician-diagnosed comorbidities (Supplementary Table 1, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.22678/abstract). A purposeful selection method was used for identifying variables to be considered for the multivariate models; that is, we included in the multivariate model only variables that had some association with the outcome variable (i.e., had a P value of ≤ 0.10, which was the prespecified threshold). The selection of the final model was based on evaluation of overall model fit statistics and included an iterative model selection (backward as well as stepwise) process and examination of variables that were associated with outcomes.

Analyses were conducted using SAS PROC MIXED and PROC GENMOD procedures for continuous and categorical outcome variables.

RESULTS

Baseline characteristics of the 1,297 included subjects (n =1,067 women [82.3%]) are summarized in Table 1. The mean ± SD age was 56.6 ± 14.1 years, and the mean ± SD symptom duration was 15.3 ± 13.0 years. Most patients (70.7%) were seropositive and/or had received DMARDs (86.7%), with some patients receiving bioDMARDs (n = 477, 36.8% of entire population) at baseline. In addition, some patients had DAS28-CRP <2.6 (n = 389, 30.0%), SDAI ≤ 3.3 (n = 91, 7.0%), or CDAI ≤ 2.8 (n = 134, 10.3%) at baseline.

Primary outcome measure: physical functioning (M-HAQ). Subjects who achieved target measures of disease activity (i.e., DAS28-CRP <2.6, SDAI ≤ 3.3, and CDAI ≤ 2.8)

Table 1. Baseline characteristics*

Characteristic	Mean ± SD or no. (%)
Age, years (n = 1,297)	56.6 ± 14.1
Symptom duration, years (n = 1,286)	15.3 ± 13.0
Body mass index, kg/m^2 (n = 1,227)	26.8 ± 5.7
Diastolic blood pressure, mm Hg (n = 1,157)	75.8 ± 10
DAS28-CRP (n = 1,255)	3.8 ± 1.6
Swollen joints, total (n = 1,295)	6.9 ± 7.2
Painful joints, total (n = 1,295)	7.7 ± 7.9
Total swollen and painful joints (n = 1,295)	14.7 ± 14.2
Female sex (n = 1,297)	1,067 (82.3)
Anti-CCP positive (n = 1,117)	703 (62.9)
RF positive (n = 1,092)	693 (63.5)
Seropositive (n = 1,128)	797 (70.7)
M-HAQ (n = 1,220)	0.43 ± 0.46
RA disease target measures (n = 1,297)	
DAS <2.6	389 (30.0)
CDAI ≤2.8	134 (10.3)
SDAI ≤3.3	91 (7.0)
DMARD at baseline (n = 1,297)	1,124 (86.7)
Biologic DMARD at baseline (n = 1,297)	477 (36.8)

* DAS28-CRP = Disease Activity Score in 28 joints using the C-reactive protein level; anti-CCP = anti–cyclic citrullinated protein; RF = rheumatoid factor; M-HAQ = modified Health Assessment Questionnaire; RA = rheumatoid arthritis; CDAI = Clinical Disease Activity Index; SDAI = Simplified Disease Activity Index; DMARD = disease-modifying antirheumatic drug.

experienced improved physical functioning on the M-HAQ compared to subjects who did not attain these target measures (Figure 1). In addition, BRASS registrants with incrementally worse disease activity levels (i.e., LDA, MDA, and SDA) experienced decreased physical functioning on the M-HAQ compared to patients attaining the foregoing target measures (Figure 2). After controlling for baseline covariates in the mixed models, we found that achievement of DAS28-CRP <2.6 was associated with a mean reduction (improvement) of 0.0823 in M-HAQ scores ($P < 0.0001$) compared to not achieving DAS28-CRP <2.6. Similarly, achieving (versus not achieving) SDAI ≤3.3 or CDAI <2.8 was associated with reductions in M-HAQ scores of 0.0834 ($P < 0.0001$) and 0.1035 ($P < 0.0001$), respectively (Table 2).

Compared to individuals with LDA, subjects who achieved these target measures of disease activity had mean reductions (improvements) on M-HAQ scores of 0.0221 ($P = 0.1735$), 0.0471 ($P = 0.0100$), and 0.0734 ($P = 0.0003$) based on DAS28-CRP, SDAI, and CDAI criteria, respectively. When compared to individuals with MDA, subjects achieving these same target measures of disease activity experienced mean reductions on M-HAQ scores of 0.0875 ($P < 0.0001$), 0.0909 ($P < 0.0001$), and 0.1192 ($P < 0.0001$) based on DAS28-CRP, SDAI, and CDAI criteria, respectively. Similar findings on physical functioning were observed in BRASS registrants achieving the target measures of disease activity compared to SDA (Table 2): significant improvements in M-HAQ across DAS28-CRP, SDAI, and CDAI categories ($P < 0.0001$ for each comparison).

Other covariates significantly associated with improved M-HAQ scores across all 3 composite measures included prior treatment with methotrexate (MTX), lower baseline M-HAQ score (i.e., less physical dysfunction at baseline), shorter RA duration, an absence of osteoporosis, and being a former (versus current) smoker (Supplementary Table 2, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.22678/abstract).

Secondary outcome measures: HRQOL (EQ-5D) and health care resource use. Similar findings to the M-HAQ were evident concerning HRQOL on the EQ-5D and health care resource use (DME and hospitalizations). Subjects who achieved guideline-recommended target measures of disease activity experienced enhanced HRQOL and decreased resource use, compared to those who did not attain these targets, during each year of followup (Figure 1). (Numbers of patients who achieved [or did not achieve] targets at each time point are tabulated in Supplementary Table 3, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.22678/abstract).

Conversely, with each increasing (worsening) measure of disease activity (i.e., LDA, MDA, and SDA), subjects experienced decreased HRQOL and increased resource use compared to their counterparts who achieved the target measures (Figure 2). After controlling for baseline covariates in mixed models, we found that subjects who achieved (versus did not achieve) the foregoing target measures of disease activity experienced significant improvements on the EQ-5D across all 3 composite indices, with increases of 0.0478 to 0.0735 ($P < 0.0001$ for each) (Table 2). Subjects who achieved the target measures of disease activity for DAS28-CRP, SDAI, and CDAI experienced significantly improved HRQOL compared to individuals with LDA, MDA, or SDA (each $P < 0.0030$).

Subjects who attained guideline-recommended target measures of disease activity also had significantly (or borderline significantly) lower odds of DME use and hospitalization (Table 3). The odds of DME use in subjects who achieved (versus did not achieve) the targets was reduced by approximately 23–45% for DAS28-CRP <2.6 (odds ratio [OR] 0.77, $P = 0.0086$), SDAI ≤3.3 (OR 0.61, $P = 0.0011$), and CDAI ≤2.8 (OR 0.55, $P = 0.0002$). Reductions in the odds of DME use were also observed when subjects achieving target measures were compared to those with LDA on the SDAI and CDAI, with decreases of 36–39%. Across all 3 disease measures, subjects who achieved the desired targets had significantly reduced odds of DME use compared to individuals with SDA (reductions of 40–55%; $P < 0.0090$ for each comparison) (Table 3).

Findings on the odds of hospitalization were similar to the data on DME use (Table 3). The odds of hospitalization were significantly decreased, by approximately 36–45%, among subjects who achieved (versus did not achieve) the target measures of disease activity. Similar, significant reductions in the odds of hospitalization were also observed when comparing subjects who achieved the desired targets to their counterparts with MDA or SDA (but not LDA) across all measures.

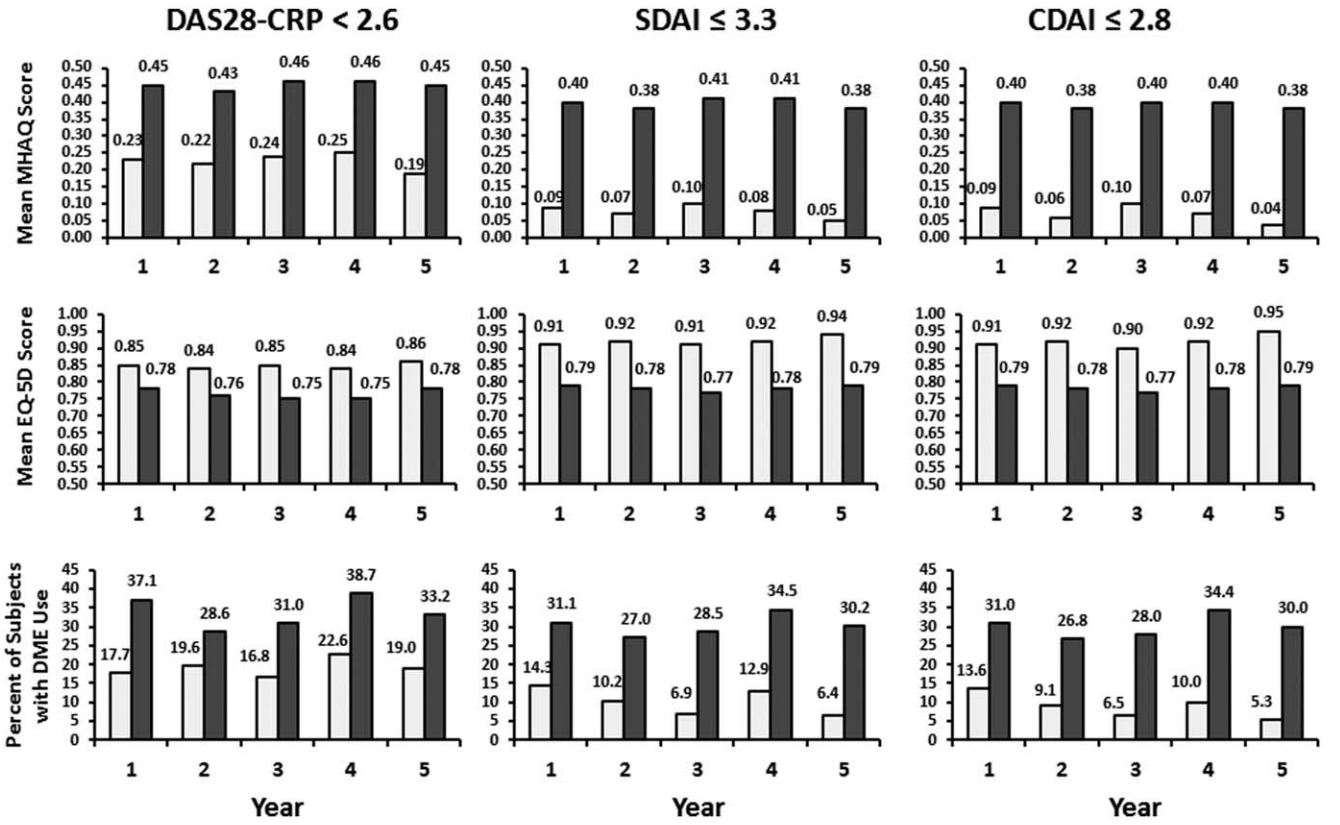

Figure 1. Mean modified Health Assessment Questionnaire (MHAQ) disability scores, EuroQol 5-domain (EQ-5D) health-related quality of life scores, and durable medical equipment (DME) use among patients achieving targets (light bars) compared to those not achieving target measures (dark bars). Disease targets were Disease Activity Score in 28 joints using the C-reactive protein level (DAS28-CRP) <2.6, Simplified Disease Activity Index (SDAI) ≤3.3, or Clinical Disease Activity Index (CDAI) ≤2.8. For numbers of patients who achieved (or did not achieve) the target at each time point, see Supplementary Table 3, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.22678/abstract.

As with the M-HAQ data, baseline covariates significantly associated with improved HRQOL on the EQ-5D included lower M-HAQ scores (i.e., less physical dysfunction) and shorter RA duration across all 3 disease measures (Supplementary Table 4, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.22678/abstract). A history of MTX therapy was also associated with a significant improvement in EQ-5D (increase of 0.018; $P \leq 0.0021$) for DAS28-CRP <2.6 but was not uniformly significantly associated with improvements in EQ-5D according to SDAI or CDAI disease targets ($P > 0.07$ for each).

DISCUSSION

This longitudinal observational cohort study demonstrated that achieving (versus not achieving) guideline-recommended target measures of disease activity of DAS28-CRP <2.6, SDAI ≤3.3, and/or CDAI ≤2.8 was associated with significant improvements in physical functioning, HRQOL, and health care resource utilization. Our findings are consistent with consensus guidelines, which have been evolving toward a strategy of treating RA to targets. Recently, a European League Against Rheumatism panel stated that LDA "defined by composite measures is a good alternative goal for...patients who cannot attain remission even today, especially those with long-standing disease who...constitute the majority of patients in clinical care" (5).

In this context, subjects who achieved the most desirable target of DAS28-CRP < 2.6 in our study did not differ significantly compared to those with LDA (2.6 ≤ DAS28-CRP <3.2) in terms of physical functioning as measured by the M-HAQ. Attainment of DAS28-CRP <2.6, SDAI ≤3.3, or CDAI ≤2.8 did not result in significant reductions in hospitalization compared to achievement of LDA (although there were trends toward reduced odds of hospitalization in subjects achieving target measures across all 3 indices) but did differ in HRQOL and DME use (significant or borderline significant differences between DAS28-CRP <2.6, SDAI ≤3.3, or CDAI ≤2.8 versus LDA, MDA, or SDA). Our findings therefore suggest that differentiation on outcome measures for achieving target measures versus LDA is not uniform. We also observed that attainment of LDA (versus MDA or SDA) was associated with favorable clinical and economic outcomes.

Most of the differences in outcomes observed between groups were both statistically significant and clinically relevant, in that they met minimum important differences (MIDs). Even though there is no consensus concerning the MID for M-HAQ in clinical practice settings, a −0.09 change

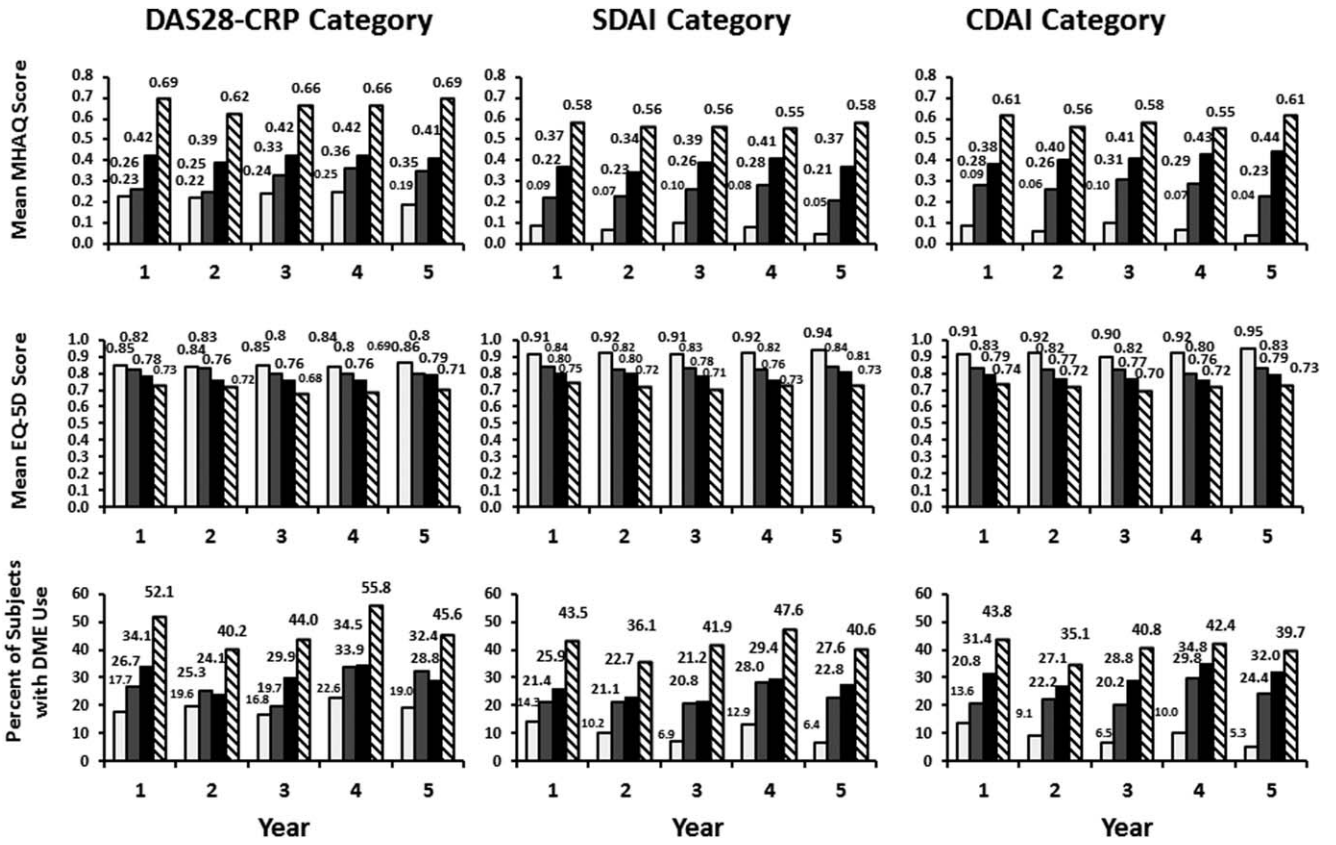

Figure 2. Mean modified Health Assessment Questionnaire (MHAQ) disability scores, EuroQol 5-domain (EQ-5D) health-related quality of life scores, and durable medical equipment (DME) use among patients with Disease Activity Score in 28 joints using the C-reactive protein level (DAS28-CRP) <2.6, Simplified Disease Activity Index (SDAI) ≤3.3, or Clinical Disease Activity Index (CDAI) ≤2.8 (light bars) compared to low disease activity (dark bars), moderate disease activity (black bars), and severe disease activity (striped bars). Low disease activity = 2.6 < DAS28-CRP ≤3.2; 3.3 < SDAI ≤11.0; 2.8 < CDAI ≤10.0. Moderate disease activity = 3.2 < DAS28-CRP ≤5.1; 11.0 < SDAI ≤26; 10.0 < CDAI ≤22.0. Severe disease activity = DAS28-CRP >5.1; SDAI >26.0; CDAI >22.0.

in the HAQ disability index has been associated with "somewhat improved" outcomes (38). Assuming that a change of −0.09 is the MID for M-HAQ, most of the comparisons in Table 2 either approach or exceed this threshold, except for comparisons between achieving guideline-recommended disease targets and LDA, where only the CDAI-based comparisons approached this difference.

To our knowledge, no investigators have reported a MID for the EQ-5D in RA. However, work done in other disease states indicates that the MID is a change of 0.05–0.08 on

Table 2. Improvements in physical functioning (M-HAQ) and quality of life (EQ-5D) based on achieving target measures of disease activity by different definitions*

	DAS28-CRP categories	*P*	SDAI categories	*P*	CDAI categories	*P*
Mean difference in M-HAQ based on…						
Achieving target (vs. not achieving)	−0.0823	< 0.0001	−0.0834	< 0.0001	−0.1035	< 0.0001
Achieving target (vs. achieving LDA)	−0.0221	0.1735	−0.0471	0.0100	−0.0734	0.0003
Achieving target (vs. achieving MDA)	−0.0875	< 0.0001	−0.0909	< 0.0001	−0.1192	< 0.0001
Achieving target (vs. achieving SDA)	−0.2040	< 0.0001	−0.1476	< 0.0001	−0.1611	< 0.0001
Mean difference in EQ-5D based on…						
Achieving target (vs. not achieving)	0.0478	< 0.0001	0.0658	< 0.0001	0.0735	< 0.0001
Achieving target (vs. achieving LDA)	0.02247	0.0026	0.05180	< 0.0001	0.06117	< 0.0001
Achieving target (vs. achieving MDA)	0.05143	< 0.0001	0.06656	< 0.0001	0.08014	< 0.0001
Achieving target (vs. achieving SDA)	0.08492	< 0.0001	0.09145	< 0.0001	0.09602	< 0.0001

* Targets: Disease Activity Score in 28 joints using the C-reactive protein level (DAS28-CRP) <2.6, Simplified Disease Activity Index (SDAI) ≤3.3, or Clinical Disease Activity Index (CDAI) ≤2.8. Low disease activity (LDA): 2.6 < DAS28-CRP ≤3.2; 3.3 < SDAI ≤11.0; 2.8 < CDAI ≤10. Moderate disease activity (MDA): 3.2 < DAS28-CRP ≤5.1; 11 < SDAI ≤26; 10 < CDAI ≤22. Severe disease activity (SDA): DAS28-CRP >5.1; SDAI >26.0; CDAI >22. M-HAQ = modified Health Assessment Questionnaire; EQ-5D = EuroQol 5-domain.

Table 3. Improvements in resource utilization based on achieving target measures of disease activity by different definitions*

	DAS28-CRP categories	95% CI	SDAI categories	95% CI	CDAI categories	95% CI
ORs for DME use based on…						
Achieving target (vs. not achieving)	0.77	0.64–0.94	0.61	0.46–0.82	0.55	0.40–0.75
Achieving target (vs. achieving LDA)	0.79	0.60–1.00	0.64	0.46–0.88	0.61	0.43–0.86
Achieving target (vs. achieving MDA)	0.84	0.67–1.00	0.70	0.50–0.96	0.55	0.39–0.77
Achieving target (vs. achieving SDA)	0.60	0.45–0.80	0.51	0.37–0.70	0.45	0.32–0.63
ORs for all-cause hospitalization based on…						
Achieving target (vs. not achieving)	0.64	0.51–0.80	0.61	0.46–0.82	0.55	0.40–0.75
Achieving target (vs. achieving LDA)	0.73	0.51–1.05	0.73	0.44–1.21	0.66	0.40–1.10
Achieving target (vs. achieving MDA)	0.72	0.54–0.95	0.55	0.33–0.91	0.55	0.33–0.92
Achieving target (vs. achieving SDA)	0.38	0.27–0.52	0.39	0.24–0.64	0.44	0.27–0.27

* Targets: Disease Activity Score in 28 joints using the C-reactive protein level (DAS28-CRP) <2.6, Simplified Disease Activity Index (SDAI) ≤ 3.3, or Clinical Disease Activity Index (CDAI) ≤ 2.8. Low disease activity (LDA): $2.6 <$ DAS28-CRP ≤ 3.2; $3.3 <$ SDAI ≤ 11.0; $2.8 <$ CDAI ≤ 10. Moderate disease activity (MDA): $3.2 <$ DAS28-CRP ≤ 5.1; $11 <$ SDAI ≤ 26; $10 <$ CDAI ≤ 22. Severe disease activity (SDA): DAS28-CRP > 5.1; SDAI >26.0; CDAI >22. 95% CI = 95% confidence interval; ORs = odds ratios; DME = durable medical equipment.

the EQ-5D (39). Based on a MID of 0.05, all comparisons in our analysis evaluating attainment of target versus LDA, MDA, and SDA (based on CDAI and SDAI) crossed the MID. On the other hand, consistent with the M-HAQ-based analyses, DAS28-CRP-based comparisons crossed or approached the MID, with the exception of attaining target compared to LDA. Taken together, these findings support both the value of treating to targets and the assertion that LDA is a plausible alternative clinical objective for treat-to-target strategies when guideline-recommended goals cannot be achieved in clinical practice.

In our study, previous treatment with MTX was associated with significantly enhanced physical functioning on the M-HAQ, while duration of RA, baseline M-HAQ, current (versus former) smoking, and osteoporosis (versus absence of osteoporosis) were associated with significantly worse physical functioning. These findings extend data from a Swedish case–control study, which determined that smoking was dose dependently associated with occurrence of anti–cyclic citrullinated peptide (anti-CCP) antibodies (40). An interaction between HLA–DR shared epitope genes and smoking triggered immune responses only in patients positive for anti-CCP. In this context, most of our patients (63%) were anti-CCP positive at baseline. Finally, a study of patients with LDA or MDA revealed a significant association between radiographic damage in RA and low femoral-neck bone mineral density (41).

All outcome measures did not perform consistently in discriminating dependent variables of physical functioning, HRQOL, and health care resource utilization across guideline-recommended target measures and levels of disease activity in our study. Previous reports indicated that data from all 3 indices are overall highly intercorrelated and show similarly high C-statistics (area under the curve values >0.80) for receiver operating characteristic curves when using, as "gold standards," clinicians' decisions either to initiate DMARDs or to increase their doses. The SDAI and CDAI include both patient and evaluator ratings of global disease activity, which are frequently discrepant (36). Perhaps the inclusion of both perspectives on global disease activity in the SDAI and CDAI (but not DAS28-CRP) renders these indices more effective assessments of physical functioning on the M-HAQ (versus DAS28-CRP).

Data concerning improvements in patient-reported and resource use outcomes based on achievement of specific levels of disease activity in patients with established or chronic RA are limited. Most studies were conducted in subjects with recent-onset RA (26–28,42,43). Unlike many RCTs involving individuals with recent-onset RA, the BRASS Registry was an observational cohort study that included subjects with a mean age of 56.6 years and a mean RA duration of 15.3 years. At baseline, the mean DAS28-CRP was 3.8 (consistent with moderate RA), fewer than 11% of subjects were in CDAI or SDAI remission, approximately 87% received conventional DMARDs, and 37% received bio-DMARDs. Given these characteristics, we consider our findings to be generalizable to most established RA populations typically encountered in clinical practices.

To our knowledge, this is the only study that formally evaluated associations between achievement of guideline-recommended targets and the likelihood of using durable equipment, such as canes, walkers, and wheelchairs. Utilization of DME was significantly (or borderline significantly) reduced in subjects with DAS28-CRP <2.6, SDAI ≤ 3.3, or CDAI ≤ 2.8 (versus LDA, MDA, or SDA on each of these measures). BRASS registrants who achieved (versus did not achieve) guideline disease targets were at significantly (up to 45%) reduced odds of DME use and hospitalization. The magnitudes of these benefits were stronger with SDAI and CDAI compared to DAS28-CRP for DME use.

In a somewhat similar, but smaller ($n = 356$), study of patients with established RA, Radner et al recently demonstrated significant benefits associated with achieving a guideline-recommended disease target (versus LDA) in subjects with a baseline mean age of 59.9 years and a mean disease duration of 11.5 years (6). This trial assessed changes in dependent variables, including physical functioning, HRQOL (by EQ-5D and Short Form 36 health survey), worker productivity, overall activity impairment, and health care costs, as functions of the independent variable of

achieving SDAI ≤3.3 (versus LDA or moderate to severe disease activity [SDAI >11]) but not the other disease targets evaluated in our study (i.e., DAS28-CRP and CDAI). Unlike our investigation, the study by Radner et al pooled data for patients with MDA and SDA because there were small numbers of patients with SDA. Patients achieving SDAI ≤3.3 in the investigation by Radner and colleagues had significantly better physical functioning, work productivity, and superior HRQOL compared to those achieving LDA. When explaining their findings, the authors suggested that the long RA duration may have resulted in an overall very disabled cohort. In this same European study, subjects with more severe levels of disease had higher total direct costs, as well as costs for both sick leave and disability (6). These findings were extended by the Dutch Rheumatoid Arthritis Monitoring (DREAM) study, which demonstrated a larger gain in quality-adjusted life years with a treat-to-target (versus usual care) clinical approach and an incremental cost-effectiveness ratio of €3,591 per subject in remission after 2 years with the treat-to-target strategy (7).

The observational nature of our study permitted enrollment of a large number of subjects who were followed over prolonged intervals (up to 5 years). In theory, our findings may have been influenced by selection bias, in that patients who responded to postal surveys and/or visited clinics to measure disease activity might have differed from nonrespondents. DME use and hospitalization were self-reported, opening the possibility of recall bias or nonrandom missing values. Nonrandom patient attrition could also have introduced biases. A previous study of the BRASS Registry identified disease duration, disease activity, and differences in drug therapy to be associated with attrition. However, during the years included in the current analysis, patient followup in the BRASS Registry was highly acceptable (32). Of approximately 1,300 patients enrolled in the BRASS Registry, 83% had followup data at year 1, 78% at year 2, 73% at year 3, 77% at year 4, and 76% at year 5. Hence, we believe that the impact of patient attrition on the findings of our analysis was small.

Findings from observational studies are typically more generalizable to usual care settings compared with RCTs. On the other hand, observational analyses are of an inherently associational nature and cannot conclusively assign causality or rule out certain biases, even though we controlled for all relevant baseline covariates. Longitudinal studies such as ours are also potentially subject to limitations related to missing data. Outcome measures within a single individual over time are also intercorrelated. To handle these issues, mixed models such as those employed in our study represent potentially advantageous approaches because all available data are included, irrespective of whether subjects had unequal numbers of observations or unequal time intervals between them.

Finally, we did not evaluate associations between achievement of different disease cut points and other patient-reported outcomes, such as pain, depression, anxiety, or fatigue, as well as objective measures such as radiographic progression.

In conclusion, this longitudinal observational study of a typical RA cohort (BRASS Registry) demonstrated benefits of treat-to-target strategies, with clinical objectives of DAS28-CRP <2.6, SDAI ≤3.3, and CDAI ≤2.8, in enhancing physical function and HRQOL, as well as reducing DME use and hospitalization. Evidence also supported the value of treat-to-target strategies with an objective of low (versus moderate or severe) disease activity. Our findings are compatible with the use of guideline-recommended target measures of disease activity as treatment objectives in clinical practice as well as LDA in patients who cannot attain guideline-recommended targets. Additional studies are needed to evaluate associations between achievement of different target measures of disease activity and other patient-reported (e.g., pain, fatigue) and radiographic (e.g., total Sharp score) outcomes, as well as actual costs rather than the odds of DME use and hospitalization, in other typical clinical settings.

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. Dr. Alemao 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.

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