Functional Status and Radiographic Joint Damage Are Associated with Health Economic Outcomes in Patients with Rheumatoid Arthritis

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ABSTRACT. ***Objective.*** This analysis examines the relationship between the functional and radiographic measures of disease activity and the employment status in patients with rheumatoid arthritis (RA). We also assessed the influence of improvement in physical function on employability, healthcare costs, and quality of life, utilizing data collected in the ATTRACT trial.

Methods. During the ATTRACT trial, the Health Assessment Questionnaire (HAQ) disability index, radiographic damage measured by the van der Heijde modified Sharp (vdH-Sharp) score, employment status, healthcare resource utilization, and quality of life measured by Medical Outcomes Survey Short Form-36 were assessed at baseline and again periodically through Week 54. Clinically important improvement was defined as an improvement in the HAQ of ≥ 0.25 from baseline to Week 54.

Results. There was a significant association at baseline between functional status and the percentages of patients employed. Increased radiographic joint damage was associated with lower fulltime employment rate, with patients in the 2 highest quartiles (vdH-Sharp score > 51.5) of radiographic damage having lower rates of fulltime employment than those with less damage. During the ATTRACT trial, patients who achieved a clinically important improvement in HAQ scores had a significant improvement in their employability (21% vs 3%; p < 0.001), in their time lost from work (7 vs 30 days; p = 0.012), in their total/direct medical costs (US$7093/$6791 vs $11,712/$10,039; p < 0.001), and in their quality of life (p < 0.001) compared with those who did not demonstrate this improvement.

Conclusion. Functional disability and radiographic joint damage are correlated with employment in patients with RA. Clinically important improvement in HAQ scores is associated with substantial health economic and quality of life benefits for patients with RA. (J Rheumatol 2004;31:849–55)

Key Indexing Terms:
HEALTH ECONOMICS   EMPLOYABILITY   DISABILITY   RHEUMATOID ARTHRITIS
HEALTH ASSESSMENT QUESTIONNAIRE   RADIOGRAPHIC DAMAGE

Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory disorder of unknown etiology that affects roughly 1% of the population worldwide[1]. Eighty percent of RA cases occur between the ages of 35 and 50 years, which are often prime years for earning potential at work[2]. RA can be associated with substantial morbidity, and often interferes considerably with the ability to perform activities of daily living. Thus, patients with RA may be at risk for work disability, particularly when the disease is chronically active and severe. Of note, it has been shown that almost half of patients with RA experience work disability as a result of RA within 10 years after diagnosis[3]. Thus, RA represents a tremendous economic burden, not only for patients and their families, but also for society as a whole[4-8]. The societal costs related to RA are diverse, and include the indirect costs resulting from a loss of productivity and the direct medical costs related to the treatment of RA, including hospitalizations and orthopedic surgery[7-11]. A therapeutic intervention that could effectively prevent or reverse disease progression in RA, and at the same time improve patients' physical functioning, might be expected to obviate many of these costs.

The Health Assessment Questionnaire (HAQ) has been widely used to evaluate the physical functioning of patients with RA in clinical trials and clinical practice[12,13]. The HAQ is a 20-question instrument that assesses the degree of difficulty a patient has in accomplishing tasks in 8 functional areas (dressing, arising, eating, walking, hygiene, reaching, gripping, and activities such as performing errands and chores). The HAQ scores range from 0 to 3, with higher scores representing greater disability. To be of value, effec-

tive treatments should result in a change in physical functioning that is not only statistically significant but also clinically meaningful, i.e., an improvement that a typical patient should be able to notice after treatment[14,15]. An improvement of 0.25 in HAQ has been found to be clinically meaningful[14]. However, to what extent achieving such a clinically meaningful improvement in physical functioning might be associated with significant economic benefits resulting from improvement in patients' employability and reduced medical costs has not been evaluated. It has been shown that functional status as measured by the HAQ is associated with employment[11,16], and is also a good predictor of future work disability[3,11]. Patients with higher HAQ scores, indicating more disability, have greater healthcare resource utilization and incur higher medical costs[5,9,10]. However, studies to date have not examined whether a clinically meaningful improvement in the HAQ is associated with improvement in employment status, or with any reduction in healthcare costs.

Joint damage as assessed by radiography is often considered as a hallmark of severe RA[17]. It has been shown that over time, there is a correlation between functional status and radiographic damage[18,19]. Interestingly, there are very limited data available on the relationship between joint damage and employment. Prevention of functional disability and joint damage has become an important goal in treating RA. Because measures of these outcomes are commonly included in clinical trials, understanding the association between these measures and economic outcomes is essential in assessing the value of new treatments.

We evaluated the associations between functional disability, radiographic joint damage, and employment status at baseline among patients with RA who were enrolled in the ATTRACT (Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy) trial. We also assessed the impact of improved physical functioning after effective treatment in the ATTRACT trial on patients' employability, overall healthcare costs, and quality of life. Our hypothesis was that an improvement in HAQ would result in improvements in health economic outcomes, regardless of treatment received.

MATERIALS AND METHODS

Study design. Detailed descriptions of the ATTRACT study design have been published[20,21]. Briefly, RA patients who had active disease despite the use of concomitant methotrexate (MTX) were randomly assigned to receive MTX or one of 4 infliximab treatment regimens (3 mg/kg or 10 mg/kg every 4 or 8 weeks, after a 3-infusion induction phase) combined with MTX. Treatment outcomes were collected from baseline through Week 54 at 4-week intervals.

Radiographs of hands and feet were obtained at baseline, Week 30, and Week 54. Structural damage was assessed at these time points using the van der Heijde modification of the Sharp score (vdH-Sharp score; range 0–448)[22]. Quality of life was evaluated by physical and mental component summary scores as measured by the Medical Outcomes Survey Short Form-36 (SF-36)[23]. Disease activity was also assessed using the modified Disease Activity Score using a 28-joint count (DAS28). The DAS28 was calculated as: 0.56*SQRT (tender joint count) + 0.28*SQRT (swollen joint count) + 0.7ln(ESR) + 0.014*(patient global assessment of disease activity)[24].

Costs. Cost data commonly used for health economic evaluation[25] were collected every 4 weeks through Week 54 during the ATTRACT study. This information was used to estimate direct and indirect costs. Data were included only if they were unrelated to participation in the study. For example, office visits and laboratory testing that were performed according to the requirements of the study protocol were not included in the analysis. For direct costs, data included physician office visits, emergency room visits, home nursing visits, household assistance requirements, hospitalizations (with frequency, length of stay and intensive care unit days recorded), and medications other than study drugs. Where possible, for example for over-the-counter medications and medical equipment, actual patient-reported costs were used. For other items, costs in 1998 US dollars were obtained using published and unpublished cost data (Table 1). Indirect costs were based on self-reported time lost from work by the patient and/or the patient's caregiver.

Employment. Patient self-reported employment including full-time and part-time employment status was collected at each visit using a questionnaire. Patients who were not employed were asked if they were able to work if a job were available. Patient's employability was classified into "unemployable" if patient was unemployed and felt unable to work even if a job was available; or "employable" if patient was employed or felt well enough to work if a job were available.

Statistical methods. Based on previous studies, clinically important improvement in the HAQ was defined as an improvement of HAQ of ≥ 0.25 from the baseline to 54 weeks after treatment[14]. The patients were divided into 2 groups based on whether patients achieved or did not achieve a clinically important improvement in the HAQ. Data for patients who were over 65 years old (n = 55) or who did not have baseline data (n = 6) were excluded from the analysis of employability. Missing values were assigned the value from the most recent visit available (last-observation carried-forward method).

McNemar's test and Cochran-Armitage trend test were used to examine percentage difference and the trend of employment by change in HAQ and radiographic joint damage, when applicable. A logistic regression model was used to adjust for confounding effects of age, sex, and disease activity on employment, and to estimate odds ratio (OR) and 95% confidence interval (CI). Stepwise selection method was used to select variables with statistically significant contribution to the logistic regression model. Nonparametric Wilcoxon rank-sum tests were employed to test statistical differences in costs and time lost from work between the groups. Analyses were performed using the SAS system (SAS Institute, Cary, NC, USA). All statistical tests were 2-sided and performed at α = 0.05.

RESULTS

In the ATTRACT study, 428 patients (332 female, 96 male) were enrolled. About 64% (272/427) of all patients achieved a clinically important improvement in HAQ scores at Week 54. There were no statistically significant differences in baseline clinical and demographic characteristics between patients who achieved a clinically important improvement in HAQ and patients who did not achieve this level of improvement (Table 2).

Association of employment with physical function and joint damage at baseline. Baseline HAQ scores and baseline radiographic joint damage score were both significantly associated with employment (including full or part-time), fulltime employment, and employability at baseline (Figures 1 and 2). Thus, patients with greater functional disability, as evidenced by a higher HAQ score, were less likely to be

Table 1. Sources of cost data.

Cost Items	Source of Cost Data.
Physician office visits	Medicare reimbursement rate for physicians and specialists from 1998
Emergency room (ER) visits	Average ER visit cost from site survey in the study
Hospitalizations	Standard DRG reimbursement (*St. Anthony's DRG Guidebook*, 1998)
Medications	1998 average wholesale price (Mosby's *GenRX*, 1999, and *The Red Book*, 1999)
Home health care visits	Medicare database of provider fees for home nursing visit
Household assistance visits	Average wage for private household occupation from US Bureau of Labor Statistics, 1998
Over-the-counter medications and medical equipment and supplies	Actual costs reported by patient in case report form
Medical procedures	Hewitt Associates Comparative Health Claims Database, 1995–98
Patient time lost from work	Overall average wage by patient's employment category from US Bureau of Labor Statistics, 1998
Care-giver time lost from work	Average wage for private household occupation from US Bureau of Labor Statistics, 1998

Table 2. Baseline demographic and clinical characteristics of ATTRACT patients.

	Improvement in HAQ ≥ 0.25 at Week 54	Improvement in HAQ < 0.25 at Week 54	Total
No. of patients	272	155	427*
No. (%) male	62 (23)	34 (22)	96 (22.4)
Age, yrs	51.7 ± 11.4	53.8 ± 12.1	52.4 ± 11.8
Disease Activity Score	6.7 ± 1.01	6.7 ± 0.97	6.7 ± 1.0
HAQ scores	1.7 ± 0.6	1.7 ± 0.7	1.7 ± 0.6

* One patient had missing value on baseline HAQ; values presented as mean ± SD unless otherwise specified. HAQ: Health Assessment Questionnaire.
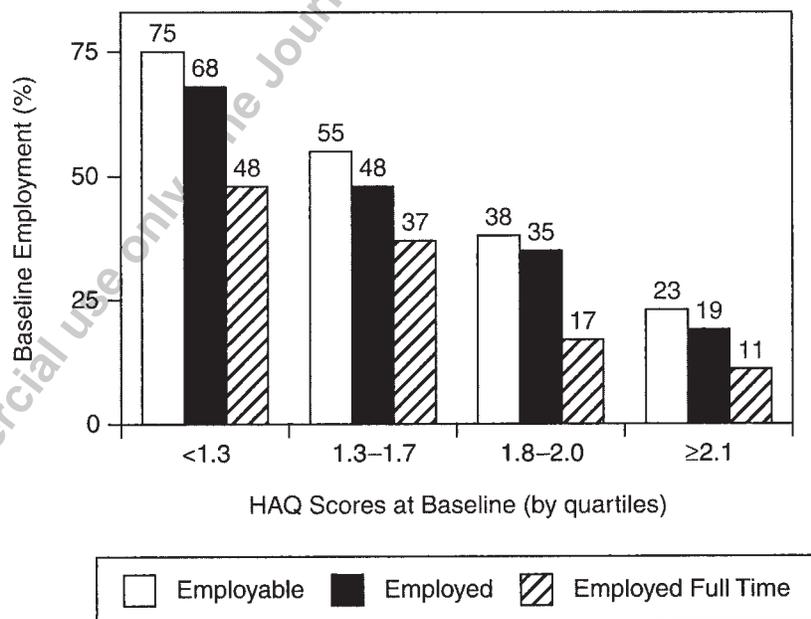

Figure 1. Age and sex adjusted employment status at baseline by HAQ scores; all p values calculated by Cochran-Armitage test for trends for employment status from the lowest to the highest quartiles of HAQ scores were p < 0.001.

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able to work upon entry to the study. After adjustment for age, sex, and disease severity score using a logistic regression model, baseline HAQ scores were statistically significantly correlated with baseline employment (fulltime or part-time) and employability (Table 3). It appeared that there was a linear trend, with higher HAQ scores yielding progressively lower employment (p < 0.001; Figure 1). Regarding joint damage, patients with more extensive damage as evidenced by higher vdH-Sharp scores were less likely to be able to work at baseline. After adjustment for age, sex, and disease severity score using a logistic regression model, baseline radiographic joint damage was statistically significantly associated with fulltime employment at baseline (Table 3). Interestingly, there appeared to be a plateau in the association, particularly regarding fulltime employment (Figure 2). Thus, fulltime employment decreased from 43% to 35% to 18% in the first 3 quartiles

of vdH-Sharp score; however, in the fourth quartile, fulltime employment did not decrease further, but remained at 19%.

Change in employability and work loss by change in HAQ. Data for the change in HAQ scores and employment were available for 368 patients aged 65 years or younger. Twenty-one percent of patients who achieved a clinically important improvement in HAQ versus 3% of patients who did not experienced a change in their employability from an unemployable status at baseline to an employable status at Week 54 (p < 0.001; Figure 3). After adjustment for baseline demographic and clinical characteristics (age, sex, Disease Activity Score, employability) using a logistic regression model, the clinically important improvement in HAQ scores after treatment was statistically significantly related to employability (employable status) at Week 54 (OR 2.65, p = 0.025). Both the high baseline HAQ scores and the high baseline radiographic vdH-Sharp scores were negatively
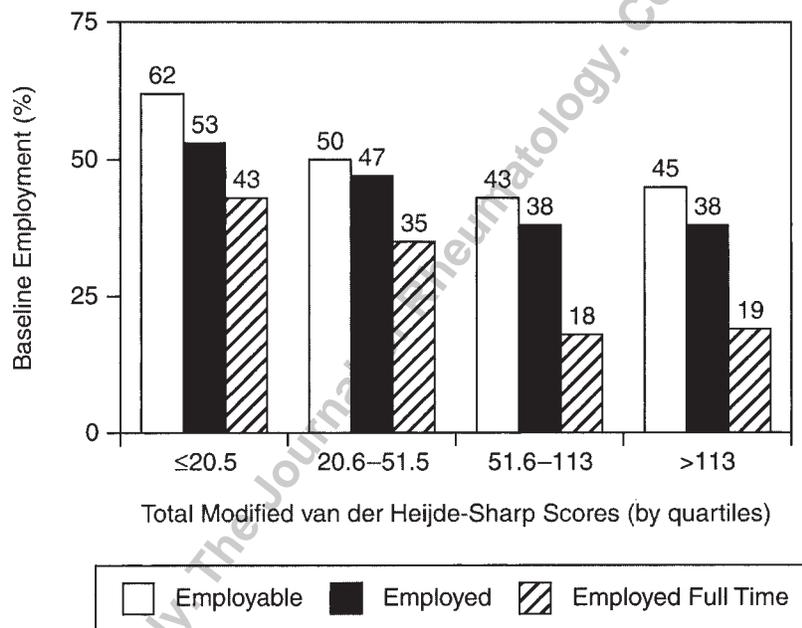

Figure 2. Age and sex adjusted employment rate at baseline by vdH-Total Sharp score; p values calculated by Cochran-Armitage test for trend for employable, employed, and fulltime employment from the lowest to the highest quartiles of total Sharp score were p < 0.003, p < 0.002, and p < 0.001, respectively.

Table 3. Factors associated with employability, all employment, and fulltime employment at baseline in the logistic regression model.

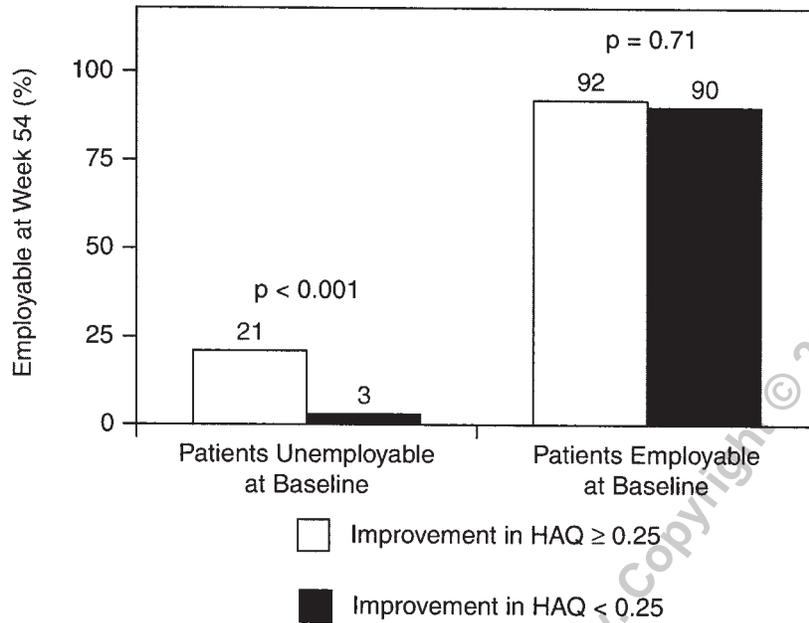| Variable	Employable		Employed		Fulltime Employed	
	ß	OR (95% CI)	ß	OR (95% CI)	ß	OR (95% CI)
Age (per year)	−0.027	0.97 (0.95–0.997)	−0.029	0.97 (0.95–0.99)	−0.041	0.96 (0.94–0.99)
HAQ scores (per unit)	−1.500	0.22 (0.15–0.34)	−1.341	0.26 (0.17–0.40)	−1.413	0.24 (0.15–0.39)
Sex (male)					0.751	2.12 (1.15–3.91)
VdH-Sharp score (per 50 units)					−0.405	0.67 (0.54–0.83)

ß: Estimated coefficient.

Figure 3. Changes in employability by improvement in HAQ scores from baseline to Week 54.

Table 4. Factors associated with employable work status at Week 54 in logistic regression model.

Variables	ß	p	OR (95% CI)
Baseline HAQ (per unit)	–1.302	< 0.001	0.27 (0.13–0.56)
Employable at baseline (yes)	4.231	< 0.001	68.8 (29.6–160.1)
Baseline vdH-Sharp score (per 50 units)	–0.382	0.007	0.68 (0.52–0.90)
Improvement in HAQ ≥ 0.25 at Week 54 (yes)	0.974	0.025	2.65 (1.13–6.21)

ß: Estimated coefficient.

related with employability (employable status) at Week 54 ($p < 0.001$ and $p = 0.007$; Table 4).

Patients with a clinically important improvement in HAQ lost, on average, less time from work (7 ± 18 days) compared with those without the improvement in HAQ (30 ± 71 days; $p = 0.012$). Patients' caregivers also lost less time from work in the group with a clinically important improvement in HAQ scores (1 ± 4 days) compared with the group without a clinically important improvement (2 ± 11 days; Table 5).

Analysis of healthcare costs during treatment by change in HAQ. The total (direct and indirect) costs and the direct cost from baseline through Week 54 for patients who achieved a clinically important improvement in HAQ scores were

Table 5. Time lost from work, direct and indirect costs, and improvement in quality of life from baseline through Week 54 by HAQ improvement.

	Improvement in HAQ ≥ 0.25 at Week 54	Improvement in HAQ < 0.25 at Week 54	p
No. of patients	272	155	
Work days lost by employed patients	7 ± 18	30 ± 71	0.012
Work days lost by caregivers	1 ± 4	2 ± 11	0.27
Total (direct and indirect) costs, $	7093 ± 22,460	11,712 ± 17,646	< 0.001
Total direct costs	6791 ± 22,392	10,039 ± 15,846	< 0.001
Total indirect cost*	302 ± 1161	1673 ± 6298	0.45
Improvement in SF-36 PCS from baseline, %	53 ± 64	8 ± 36	< 0.001
Improvement in SF-36 MCS from baseline, %	14 ± 30	5 ± 27	< 0.001

* Indirect cost from loss of productivity due to early retirement/unemployment was not included. Values presented as mean ± SD unless otherwise specified. SF-36: Short Form-36. PCS: Physical component summary scores, MCS: mental component summary scores.

$7093 and $6791, respectively. In contrast, these costs for patients who did not achieve a clinically important improvement in HAQ were $11,712 and $10,039, respectively (p < 0.001). The indirect costs resulting from lost workdays for both patients and caregivers with and without a clinically important improvement in HAQ scores were $302 and $1673, respectively (Table 5).

Change in quality of life by change in HAQ. Patients who achieved a clinically important improvement in HAQ scores showed a statistically greater improvement in the SF-36 physical and mental component summary scores, 53% ± 64% and 14% ± 36%, respectively, compared with patients who failed to achieve a clinically important improvement in HAQ, 14% ± 30% and 5% ± 27%, respectively (p < 0.001; Table 5).

DISCUSSION

Recent years have witnessed remarkable progress in our understanding of the immunopathophysiologic basis of RA and other systemic inflammatory disorders. Coupled with progress in biotechnology, this has resulted in the introduction of several important new therapies[26]. Part of the impetus for the development of novel treatments has been appreciation of the severity of RA. Not only do patients suffer substantial morbidity, they also incur substantial costs related to this pernicious disease. The costs associated with RA are associated with functional disability[19]. In theory, therapeutic interventions that prevented or reversed disease progression and improved patients' physical functioning might be expected to obviate some of the costs of the disease. Given the relatively high acquisition costs of the newer biologic therapies for RA, these considerations are particularly relevant.

The results of our analyses, using baseline data from the population of patients enrolling in the ATTRACT trial, substantiate previously published data correlating functional status and employment[11,16]. Thus, higher levels of functional disability as assessed by the HAQ are associated with lesser ability to work. Of note, this association was confirmed in a selected population, namely RA patients who were chosen based upon the activity and severity of their disease. This validates the observations previously reported in other cohorts of patients with RA. Our analyses also yielded several observations that have not been reported previously. We found a significant association between vdH-Sharp score and fulltime employment. Interestingly, the fulltime employment rate progressively decreased among the lower 3 quartiles, but was similar for the highest 2 quartiles. These results indicate that there may be a threshold of about 50 vdH-Sharp score units, above which the likelihood of fulltime employment is very low (< 20%). While radiographic scores are almost universally included in current therapeutic trials in RA[27], there have been few data available assigning any clinical relevance to the scores. The results of this analysis, along with the plethora of data demonstrating the rapidity of progression in radiographic damage early in the disease course, highlight the need for early effective intervention to halt the progression of joint damage before this threshold is reached. Of note, we also found an association between severe baseline joint damage and poor improvement in employability after treatment, emphasizing the need for earlier intervention.

Another interesting finding of this analysis is the difference between fulltime employment and any employment. The association between vdH-Sharp score and fulltime employment was strong, while the association between vdH-Sharp score and any employment was much weaker. This could potentially be because patients shift from fulltime to part-time employment as joint damage progresses. These findings underscore the importance of distinguishing between fulltime and part-time employment in any economic analyses that assess work disability in patients with RA.

Recently, there has been considerable interest in assessing the clinically important improvement in health related quality of life (HRQOL) measures in the evaluation of treatment efficacy[14,15]. It is important to establish a criterion for a clinically important improvement in HRQOL measures, since many clinicians have only recently begun to incorporate HRQOL measures in the evaluation of treatment efficacy and may need guidance to interpret changes in the HRQOL scores. A change in HAQ of 0.25 has been reported to be clinically meaningful for patients with RA[14]. The threshold for a clinically meaningful improvement in HAQ scores was derived by comparing the change in HAQ to other subjective patient-reported outcomes. Until now, this threshold has not been validated by examining its association with more objective economic outcomes. The results from this analysis show that clinically important improvement in HAQ scores is accompanied by an improvement in patients' employability and decreased medical costs, indicating that clinically important improvement in HAQ scores is also associated with important health economic benefits.

In this analysis, indirect costs were far lower than direct costs. This is in contrast to most studies in RA, where indirect costs exceed direct costs by several-fold[28]. A major part of the reason for this disparity is the conservative nature of the methods by which indirect costs were assessed. Thus, only data for patients who were actively employed during the study period were included when estimating the indirect cost resulting from loss of productivity due to disease. Of note, roughly 36% of patients in this trial had retired before age 65; however, it is not possible to determine if their early retirement was directly related to RA. If the early retirement due to disease had been taken into account in estimating costs due to loss of productivity, then the indirect cost would be much higher in this ATTRACT population.

There are several limitations to economic data collected during clinical trials. Healthcare resource utilization in the clinical trial setting can differ substantially from standard

clinical practice. Further, the patient population enrolled in the trial may not be entirely representative of the patient population with RA. Economic modeling can be a means of overcoming some of these limitations and of estimating the value of new interventions in clinical practice. Recently published models using the ATTRACT data found infliximab treatment to be cost-effective for patients who have had an inadequate response to MTX[29,30].

Notwithstanding the limitations, our results provide important insight into the relevance of improvements observed in functional and radiographic measures of disease severity in RA clinical trials. These results also underscore the importance of early intervention in order to maintain longterm functioning, employability, and quality of life in patients with RA. With the heightened interest in economic considerations, due in part to the cost of newly introduced therapies, there is a need for rigorous pharmacoeconomic assessments to establish the true value of therapies.

ACKNOWLEDGMENT

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