Short-term Influence of Adalimumab on Work Productivity Outcomes in Patients with Rheumatoid Arthritis

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ABSTRACT. ***Objective.*** To evaluate the shortterm effect of adalimumab on work productivity in patients with moderate to severe active rheumatoid arthritis (RA).

Methods. In a substudy of the Canadian Adalimumab Clinical Trial (CanAct), clinical, health status, and productivity outcomes were measured at baseline and 12 weeks. Patients were classified as responders and nonresponders by the 20% American College of Rheumatology (ACR20) improvement criterion and the minimum clinically important difference (MCID) of the Health Assessment Questionnaire (HAQ) score (0.22), respectively. The Health and Labour Questionnaire (HLQ) was used to measure productivity outcomes and costs.

Results. Included in the analysis were 389 patients completing both baseline and 12-week HLQ questionnaire. Absenteeism (a decrease of 0.5 workdays per 2 weeks) and unpaid work productivity (3.5 fewer hours unpaid help per 2 weeks) were improved significantly after 12 weeks. Improvements in productivity outcomes were associated with clinical response. Bootstrapping results suggest that responders achieved statistically significant improvement in presenteeism (ACR20) and unpaid work productivity (ACR20 and HAQ) versus nonresponders. The costs saved by responders were up to $155.04 per 2 weeks more than those by nonresponders.

Conclusion. The costs of adalimumab were partially offset, even in the short term, by cost savings induced by clinical response among Canadian patients with moderate to severe RA. These findings complement results of other study analyses that demonstrate early and sustained benefits of adalimumab. (First Release Aug 1 2008; J Rheumatol 2008;35:1729–36)

Key Indexing Terms:
RHEUMATOID ARTHRITIS ADALIMUMAB PRODUCTIVITY ECONOMICS

Rheumatoid arthritis (RA) is the most common form of inflammatory arthritis[1]. The disorder has a prevalence of about 1% and an annual incidence of 3 per 10,000 adults[2]. Traditional treatment consists of disease modifying antirheumatic drugs (DMARD) such as methotrexate (MTX). More recently, biologic DMARD, such as the tumor necrosis factor antagonists, have been approved for treating RA. Many studies have demonstrated the potential for these medications to reduce disease activity, prevent radiographic progression, and improve physical function[3,4].

The costs associated with RA are substantial. Direct costs alone have been estimated at more than US $6000 annually per patient[5]. The introduction of biologic agents has increased estimates of direct costs markedly, to close to US $20,000[5]. Consequently, whether the additional benefits associated with biologic agents are worth the additional expense has been the focus of numerous studies[4,6]. Many studies have found that these new therapies provide improvements in health status. Published reports discuss the possibility that these improvements might delay joint replacements and other hospitalizations, thereby substantially offsetting some direct costs in the long term[4-8].

However, few studies have addressed whether the new RA treatments improve work productivity outcomes. Indirect costs resulting from reduced productivity and early retirement have been reported to be even greater than direct costs of medical care[9-12]. Most studies have focused on changes in employment status and absenteeism, usually expressed as the number of absent work days, in patients taking biologic therapies[13-18]. A recent study has found that presenteeism, the measure of reduced performance while at work, rather than absenteeism, is the major contributor of

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indirect costs in patients with arthritis[19]. However, no studies, to our knowledge, have examined whether new treatments improve presenteeism[20].

Our study was designed to comprehensively evaluate the influence of adalimumab on work productivity in patients with moderate to severe active RA who participated in the Canadian Adalimumab Clinical Trial (CanAct)[21]. The 12-week changes in patients' employment status, paid work absenteeism, paid work presenteeism, and productivity in unpaid work were measured. Comparisons were made to the 12-week changes in groups of patients who responded to treatment and those who did not.

MATERIALS AND METHODS

Study design. CanAct was an open-label, multicenter, Phase IIIb study conducted in Canada. Patients with moderate to severe RA who had an inadequate response to DMARD, including MTX, were treated with adalimumab 40 mg subcutaneously every other week combined with their pre-existing therapy[21]. The main inclusion criteria were (1) subject was ≥ 18 years of age; (2) subject had a confirmed diagnosis of RA defined by ≥ 5 swollen joints and one additional criterion of positive rheumatoid factor, one or more joint erosions on radiographs, or Health Assessment Questionnaire (HAQ) score > 1; (3) subject had met the American College of Rheumatology (ACR) criteria for diagnosis of RA for at least 3 months; (4) subject had unsatisfactory response or intolerance to prior standard therapy, as required by local provincial guidelines prior to initiating biologic therapy. In a substudy of CanAct, a number of clinical, health status, and productivity outcomes were measured at baseline and 12 weeks.

Clinical and health status outcomes. Clinical outcome measures included the tender joint count, swollen joint count, physician global assessment of disease, patient global assessment of disease, patient pain assessment, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) concentration. In addition, patients' disease activity was assessed using the modified Disease Activity Score using a 28-joint count (DAS28)[22]. We focused our analysis on the influence of disease on physical disability, measured using HAQ[23,24], and clinical response, evaluated using the ACR response criteria[25]. A HAQ score difference of 0.22 was used to represent the minimum clinically important difference (MCID)[26,27].

Work productivity outcomes. We measured the effect of adalimumab on work performance and productivity using the Health and Labour Questionnaire (HLQ), a validated productivity instrument used in many diseases[28-33]. Its 4 modules include: absence from paid work, reduced productivity from paid work, unpaid labor production, and impediments to paid and unpaid labor (for a detailed description and scoring methods see Appendix). A 2-week recall period was used to measure productivity losses. Only those who had paid employment at the time of interview were required to answer the questions in Modules 1 and 2, and all patients answered questions in Modules 3 and 4.

Among all the productivity outcomes derived from the HLQ, for the objectives of our study, we focused on questions related to absenteeism (no. of absent workdays due to RA), presenteeism (no. of extra work hours patients needed to catch up on tasks they were unable to complete in normal working hours due to RA), and unpaid work productivity (no. of hours paid and unpaid help to complete tasks patients were unable to complete due to their RA disease).

Costs of work productivity losses. The costs of work productivity losses were considered from a societal perspective and measured using 2005 Canadian dollars. The human capital method was employed to calculate costs of productivity losses. The underlying assumption of this method is that workers are paid by their marginal products, and that the marginal value of leisure time is equal to how much they can earn at work, since the opportunity cost of working is the value of leisure foregone[34].

The costs of work productivity losses included 3 main components: (1) cost of absenteeism, estimated as the number of absent workdays multiplied by the individual's daily wage; (2) cost of presenteeism, estimated as the number of extra work hours patients needed to catch up on tasks they were unable to complete during normal working hours multiplied by the individual's hourly wage; and (3) cost of unpaid work, calculated by first summing numbers of hours of unpaid and paid help received by patients and then multiplying the sum by hourly wage for childcare and home support workers. The total costs of lost productivity were the sum of the 3 main components.

Average weekly and hourly gross wages of employees in Canada were used for the valuation of productivity losses. These were calculated by patients' type of work, defined using the National Occupational Classification for Statistics, and by their age and sex from the 2005 labor force survey[35]. The valuation of unpaid help was estimated using the replacement cost of hiring a paid laborer to complete the tasks. This method is valid only when output is lost altogether (i.e., when the tasks must be done by hiring a paid laborer if unpaid help is unavailable). Therefore, the chores that the patient cannot complete due to illness were neglected. The mean hourly gross wage for child care and home support workers, derived from Statistics Canada[35], was used as a proxy for the value of the marginal product of these tasks.

Statistical methods. The primary outcome of the analysis was productivity, and thus only those patients who responded to the HLQ at both baseline and 12 weeks were included. The sample size for each outcome variable was based on the valid data available at both baseline and 12 weeks.

Baseline demographic and disease-related characteristics were summarized by patients' baseline employment status. Independent t-test for continuous variables and chi-square or Fisher's exact tests for categorical variables were used to test the difference between employed patients and unemployed patients.

Changes from baseline to 12 weeks in productivity outcomes and costs of productivity losses were measured. Because the productivity outcomes were measured in a 2-week recall period, we assumed that this 2-week period was representative for the period between baseline and the 12-week visit. For categorical variables, McNemar's test or Bowker's test of symmetry was used to examine percentage changes from baseline to 12 weeks in productivity outcomes and costs, when applicable. For continuous variables, 10,000 bootstrap samples were generated to calculate the 95% bootstrapped confidence intervals (CI) for each outcome and cost measure[36]. The bootstrap p value based on t-statistics was used to test the hypotheses[36,37].

The major drawback of our study is that there is no control group. It is likely that regression to the mean plays an important role because patients with moderate to severe RA were included in this study. Further, the HLQ assesses work productivity in the previous 2 weeks and without a control group, we have insufficient insight on the natural fluctuations of worker participation over time. Therefore, to help confirm that it was the effect of the drug that produced these changes and account for the deficiency in design, we compared patients who responded to treatment with those who did not. Patients were classified as responders or nonresponders by 2 response criteria: the 20% ACR improvement criteria (ACR20) and the MCID of HAQ score (equal to 0.22), respectively. The changes from baseline to 12 weeks in productivity outcomes and costs were compared between nonresponders and responders. Similarly, we used the bootstrap method described earlier. In addition, the changes in total costs due to work productivity losses (absenteeism, presenteeism, and unpaid work productivity) were estimated for both nonresponders and responders by a linear model adjusting for the potential confounding effects of patients' demographic and disease-related characteristics.

RESULTS

The original CanAct study enrolled 879 patients, but only those who were recruited as part of amendment 3 of study protocol M02-574 were eligible for the productivity study. Of these 467 eligible patients, 389 completed both the base-

line and 12-week HLQ questionnaire. Table 1 presents the patients' baseline demographic and disease-related characteristics. On average, the patients were 55 years old and had a disease duration of more than 12 years. At baseline, 140 (36%) patients were in paid employment. Compared with patients who were not employed, these patients were younger and had a shorter duration of RA and better disease activity and physical function (Table 1).

Changes in work productivity outcomes at 12 weeks from baseline. As expected over such a short period, the employment status of patients did not change significantly within 12 weeks. Five patients (4%) were not employed at baseline but were employed at 12 weeks, and 5 patients moved in the opposite direction. Therefore, we did not include the days of work disability until retirement into analysis. Table 2 shows the changes from baseline to 12 weeks in productivity outcomes. Mean absent workdays were 1.3 days per 2 weeks at baseline and 0.8 days at 12 weeks, a significant decrease of a half-day per 2 weeks (bootstrap $p < 0.05$). In addition, patients worked 0.3 fewer extra hours per 2 weeks to catch up on tasks they were unable to complete within normal working hours, showing that work performance was improved, but the improvement was not significant. Moreover, patients spent more time on household tasks ($p > 0.05$), and fewer tasks were completed by unpaid ($p < 0.001$) and paid help ($p > 0.05$) after 12 weeks. By McNemar's test, there were significantly more patients who did not miss any workdays ($p = 0.024$), work any extra hours ($p = 0.003$), or receive any unpaid help ($p < 0.001$) or paid help ($p = 0.014$) after 12 weeks. After 12 weeks, the costs of absenteeism, presenteeism, and unpaid work were reduced by a mean of \$57.21 (bootstrapped 95% CI –30.77, 139.79), \$4.48 (–46.24, 46.51), and \$59.51 (30.50, 88.48) per 2 weeks, respectively. Overall, the reduced total costs of lost productivity were equal to \$82.18 (30.40, 132.56) per 2 weeks ($p = 0.001$). The total cost savings were mainly driven by the significant improvement on absenteeism and unpaid work productivity (unpaid help).

Changes from baseline to 12 weeks in work productivity outcomes by response criteria. When we compared the baseline characteristics between responders and nonresponders among patients who were employed at baseline, all baseline characteristics (age, mean work hours, job type, education level, HAQ, DAS28, and presenteeism) were comparable according to both response criteria, with the exception of absenteeism. The baseline absenteeism was slightly higher

Table 1. Baseline patient characteristics.

Variables	All, n = 389, mean (SD)	Employed, n = 140, mean (SD)	Not Employed, n = 249, mean (SD)	p*
Age, yrs	55.0 (11.8)	48.3 (9.7)	58.8 (11.1)	< 0.001
Duration of RA, yrs	12.5 (10.0)	10.1 (8.1)	13.9 (10.7)	< 0.001
ESR, mm/h	32.6 (25.3)	25.7 (22.4)	36.5 (26.1)	< 0.001
CRP, mg/l	22.2 (31.9)	16.6 (23.3)	25.3 (35.5)	0.004
Tender joint count	14.3 (6.8)	13.8 (7.2)	14.6 (6.7)	0.267
Swollen joint count	12.6 (5.0)	12.6 (5.5)	12.6 (4.7)	0.970
Physician global assessment	64.4 (17.1)	64.4 (17.9)	64.3 (16.7)	0.952
Patient global assessment	65.4 (23.5)	64.9 (21.1)	65.6 (24.7)	0.771
Patient pain assessment	66.4 (23.0)	65.0 (21.3)	67.2 (23.9)	0.361
DAS28	6.1 (1.2)	5.9 (1.2)	6.2 (1.2)	0.004
HAQ	1.6 (0.6)	1.4 (0.6)	1.7 (0.6)	< 0.001
	N (%)	N (%)	N (%)	
Female	304 (78.2)	97 (69.3)	207 (83.1)	0.002
Education				< 0.001
< General secondary education	200 (51.4)	48 (34.3)	152 (61.0)	
General secondary education	59 (15.2)	22 (15.7)	37 (14.9)	
Intermediate/higher vocational education	130 (33.4)	70 (50.0)	60 (24.1)	
Caucasian	360 (92.5)	126 (90.0)	234 (94.0)	0.163
Living alone	66 (17.0)	15 (10.7)	51 (20.5)	0.016
Children in household	118 (30.3)	62 (44.3)	56 (22.5)	< 0.001
No. other DMARD				0.574
0	58 (14.9)	23 (16.4)	35 (14.1)	
1	164 (42.2)	53 (37.9)	111 (44.6)	
2	124 (31.9)	49 (35.0)	75 (30.1)	
3	43 (11.0)	15 (10.7)	28 (11.2)	
MTX	112 (28.8)	36 (25.7)	76 (30.5)	0.351

* Independent t test for continuous variables; chi-square or Fisher exact test for categorical variables. CRP: C-reactive protein; DAS28: 28-joint Disease Activity Score; DMARD: disease-modifying antirheumatic drugs; ESR: erythrocyte sedimentation rate; HAQ: Health Assessment Questionnaire; MTX: methotrexate.

Table 2. Changes from baseline to 12 weeks in productivity outcomes and costs in the past 2 weeks.

	N	Baseline	12 weeks	Δ Mean (SD)	Bootstrapped 95% CI
Module 1					
No. absent workdays, mean (SD)	145	1.3 (3.1)	0.8 (2.6)	–0.5 (2.9)	(–1.0, –0.0)*
0 days, n (%)		113 (77.9)	126 (86.9)		0.024†
> 0 days, n (%)		32 (22.1)	19 (13.1)		
Module 2					
Indicator for impediments at paid work, n (%)	117				
Not at all		37 (31.6)	80 (68.4)		< 0.001††
To a degree		63 (53.9)	35 (29.9)		
Very much		17 (14.5)	2 (1.7)		
Efficiency score, mean (SD)	113	8.8 (2.9)	7.4 (2.3)	–1.4 (2.8)	(–1.9, –0.9)**
No. extra hours needed to work, mean (SD)	106	2.0 (6.3)	1.7 (8.3)	–0.3 (10.1)	(–2.1, 1.8)
0 hrs, n (%)		72 (67.9)	88 (83.0)		0.003†
> 0 hrs, n (%)		34 (32.1)	18 (17.0)		
Module 3					
No. hours spent on unpaid work, mean (SD)	389	35.2 (22.8)	36.9 (23.6)	1.7# (23.4)	(–0.6, 4.0)
No. hours unpaid help, mean (SD)	389	10.6 (17.3)	7.2 (14.1)	–3.5 (17.3)	(–5.2, –1.8)**
0 hrs, n (%)		189 (48.6)	244 (62.7)		< 0.001†
> 0 hrs, n (%)		200 (51.4)	145 (37.3)		
No. hours paid help, mean (SD)	389	1.9 (8.7)	1.6 (8.6)	–0.3 (5.6)	(–0.9, 0.3)
0 hrs, n (%)		320 (82.3)	336 (86.4)		0.014†
> 0 hrs, n (%)		69 (17.7)	53 (13.6)		
Module 4					
Impediment score at unpaid work, mean (SD)	325	3.0 (2.1)	2.1 (2.2)	–0.9 (2.1)	(–1.2, –0.7)**
Lost productivity costs					
Absenteeism, mean (SD)	145	195.17 (490.39)	137.96 (486.78)	–57.21 (525.97)	(–139.79, 30.77)
Presenteeism, mean (SD)	114	43.91 (148.34)	39.43 (208.50)	–4.48 (245.72)	(–46.51, 46.24)
Unpaid work, mean (SD)	389	196.87 (311.93)	137.35 (256.73)	–59.51 (293.69)	(–88.48, –30.50)**
Total, mean (SD)	389	283.13 (463.90)	200.94 (457.54)	–82.18 (499.67)	(–132.56, –30.40)**

Changes indicate productivity outcomes and costs at 12 weeks minus those at baseline; if not indicated, negative difference means improvement in productivity outcomes or reductions in costs. # Positive difference means improvement in productivity outcome. * Bootstrap p value based on t-statistics < 0.05; ** bootstrap p value ≤ 0.001; † McNemar's test p value; †† Bowker's test of symmetry p value.

for nonresponders than responders only according to the MCID of HAQ. Baseline DAS28 and HAQ between responders and nonresponders were also compared among all patients. This showed that baseline DAS28 was comparable between 2 groups according to both response criteria, but nonresponders had significantly higher disability level (HAQ) at baseline than responders according to the ACR20 response criterion.

Table 3 presents the changes in productivity outcomes and costs for nonresponders and responders. The change in absent workdays was not significantly different between nonresponders and responders because the absenteeism for both nonresponders and responders improved after 12 weeks. However, the change directions were different with respect to presenteesim, hours spent on unpaid work, hours of getting unpaid help, and paid help for nonresponders and responders. Using the ACR20 response criterion, responders to treatment avoided 1.7 h per 2 weeks of extra work time catching up on tasks that they were unable to complete in normal working hours. In contrast, nonresponders needed to work 2.7 h more extra time per 2 weeks after 12 weeks ($p < 0.05$). Responders also reduced the number of unpaid help hours required per 2 weeks by 5.9 to 6.1 h, but the number for nonresponders increased by 0.3 to 1.2 h ($p < 0.001$). Costs of productivity losses per 2 weeks by the response criteria ACR20 and MCID of HAQ were reduced for responders by $54.27 and $53.62 on cost of absenteeism, $39.92 and $6.24 on cost of presenteeism, and $104.95 and $98.72 on cost of unpaid work, respectively. Whereas the cost of absenteeism for nonresponders was reduced by $62.98 and $75.29, respectively, the cost of presenteeism and cost of unpaid work increased by $69.27 and $2.99, and $7.08 and $20.26, respectively. Overall, the total costs of lost productivity increased slightly for nonresponders but declined significantly for responders by both response criteria ($p < 0.05$) after 12 weeks. In total, the responders saved $145.96 (44.76, 248.20) more than nonresponders according to the ACR20 response criterion and $126.47 (32.74, 219.59) according to the MCID of HAQ.

Adjusted reductions in total costs of work productivity losses by response criteria. Figure 1 presents the changes in total costs of productivity losses in the past 2 weeks at 12 weeks from baseline by response criteria adjusted for baseline demographic and clinical characteristics. The changes in total costs of productivity losses from baseline to 12 weeks for responders were –$135.42 (95% CI –191.10,

Table 3. Changes from baseline to 12 weeks in productivity outcomes and costs in the past 2 weeks by response criteria. Changes indicate productivity outcomes and costs at 12 weeks minus those at baseline; values presented as mean (SD) unless otherwise specified.

	ACR 20			HAQ MCID		
	Nonresponders	Responders	Bootstrapped 95% CI	Nonresponders	Responders	Bootstrapped 95% CI
No. all patients, n (%)	157 (40.6)	230 (59.4)		120 (31.4)	262 (68.6)	
No. employed patients[†], n (%)	49 (33.8)	96 (66.2)		29 (20.3)	114 (79.7)	
Module 1						
No. absent workdays	–0.3 (2.4)	–0.5 (3.1)	(–0.7, 1.1)	–0.5 (2.5)	–0.5 (3.0)	(–1.1, 0.9)
Module 2						
Efficiency score	–0.3 (2.2)	–2.0 (2.8)	(0.8, 2.7)**	–1.1 (2.6)	–1.5 (2.8)	(–1.0, 1.5)
No. extra hours needed to work	2.7 (13.9)	–1.7 (7.3)	(0.8, 10.1)*	0.1 (3.7)	–0.4 (11.1)	(–2.5, 3.3)
Module 3						
No. hours spent on unpaid work[#]	0.6 (24.0)	2.6 (23.0)	(–6.8, 2.8)	–2.3 (20.8)	4.0 (24.2)	(–11.1, –1.6)*
No. hours of unpaid help	0.3 (18.2)	–6.1 (16.3)	(3.0, 10.0)**	1.2 (18.3)	–5.9 (16.4)	(3.3, 10.9)**
No. hours of paid help	0.1 (7.6)	–0.6 (3.8)	(–0.6, 2.0)	0.1 (5.5)	–0.4 (5.7)	(–0.6, 1.8)
Module 4						
Impediment score for unpaid work	–0.4 (1.8)	–1.3 (2.2)	(0.4, 1.3)**	–0.2 (1.6)	–1.3 (2.1)	(0.7, 1.5)**
Lost productivity costs						
Absenteeism	–62.98 (441.96)	–54.27 (566.23)	(–182.40, 155.22)	–75.29 (340.41)	–53.62 (568.92)	(–191.1, 132.41)
Presenteeism	69.27 (346.21)	–39.92 (170.52)	(24.23, 241.55)*	2.99 (84.04)	–6.24 (270.94)	(–60.52, 71.05)
Unpaid work	7.08 (326.15)	–104.95 (261.78)	(50.30, 172.57)**	20.26 (307.42)	–98.72 (280.72)	(54.75, 183.09)**
Total costs	4.46 (528.83)	–141.50 (473.07)	(44.76, 248.20)*	2.31 (368.69)	–124.16 (549.67)	(32.74, 219.59)*

[†] Patients were employed at baseline or at 12 weeks; if not indicated, negative difference means improvement in productivity outcomes or reductions in costs. [#] Positive difference means improvement in productivity outcome. * Bootstrap p value based on t-statistics < 0.05; ** bootstrap p value ≤ 0.001. ACR20: American College of Rheumatology criteria (improvement ≥ 20%); HAQ MCID: minimum clinically important differences for Health Assessment Questionnaire score = 0.22.

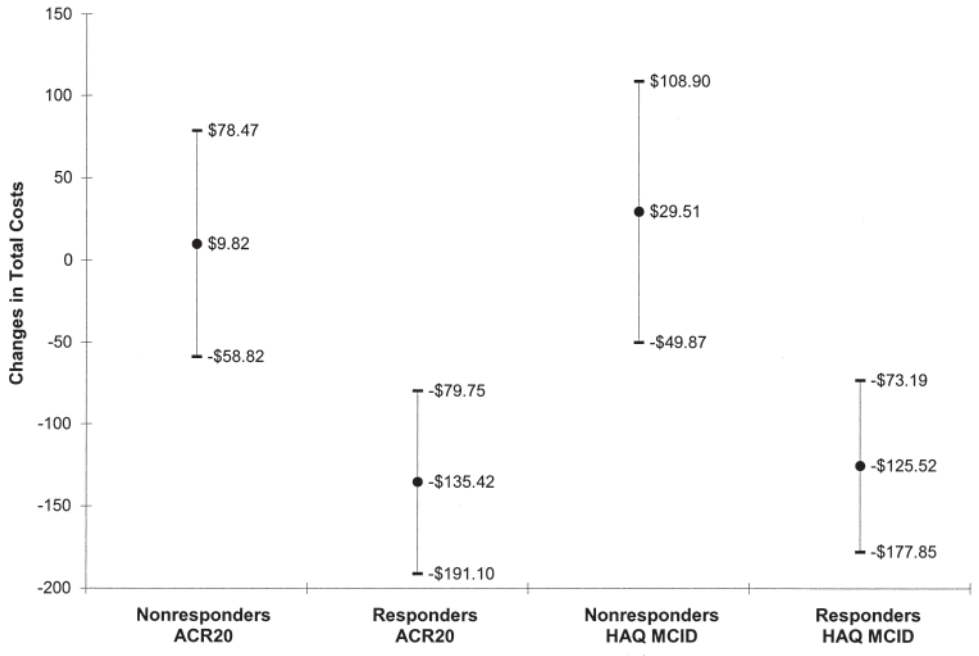

Figure 1. Adjusted changes from baseline to 12 weeks in total costs of lost productivity in the past 2 weeks by response criteria. Changes in total costs of productivity losses (the sum of cost of absenteeism, cost of presenteeism, and cost of unpaid work) in the past 2 weeks at 12 weeks from baseline were adjusted for the patients' demographic and baseline disease-related characteristics by a general linear model. Plots represent mean (95% confidence limits).

–79.75) and –$125.52 (95% CI –177.85, –73.19) per 2 weeks by the response criteria ACR20 and MCID of HAQ, respectively. In contrast, the changes for nonresponders were $9.82 (–58.82, 78.47) and $29.51 (–49.87, 108.90) per 2 weeks, respectively (p = 0.002). Therefore, the total costs saved by responders due to improved productivity were

$145.25 to $155.04 per 2 weeks more than those saved by nonresponders.

DISCUSSION

We studied the influence of the biologic DMARD adalimumab on short-term changes in productivity among patients with RA. In the 389 patients included in the final analysis, we found that absenteeism ($p < 0.05$) and unpaid work productivity (unpaid help) ($p < 0.001$) were significantly improved at 12 weeks after initiation of therapy, although there were significantly more patients who did not miss any workdays, work any extra hours, or receive any unpaid or paid help after 12 weeks. We also compared patients who responded to treatment with those who did not to help confirm that the effects of the drug produced these changes. In these analyses, the responders had significantly improved presenteeism versus nonresponders according to the ACR20 response criterion. Unpaid work productivity (unpaid help) was also demonstrated to be significantly higher for responders than nonresponders after 12 weeks ($p < 0.001$) according to both response criteria. The directions of changes on both presenteeism and unpaid work productivity (both unpaid and paid help) after 12 weeks were opposite between responders and nonresponders according to both response criteria. Nonresponders, despite the improvement in absenteeism, exhibited worsening presenteeism, as well as unpaid work productivity, after 12 weeks. On the other hand, responders presented improved absenteeism, presenteeism, and unpaid work productivity. This could explain why significant improvement on absenteeism but insignificant improvement on presenteeism was found in overall patients.

Our results show that responders had higher cost savings than nonresponders through the association of clinical response and the cost of work productivity. In our study, response was induced by adalimumab and therefore the cost of adalimumab was partially offset by cost savings since the drug induced this response (Table 2, Table 3). However, it is likely that the results would follow for any treatment that could induce similar clinical response, although this warrants confirmation. Either way, the results have important ramifications for the funding of biologic therapies. Improvements in productivity would complement direct benefits that may be realized through reductions in the signs and symptoms of RA, improvements in physical function, and inhibition of radiographic progression. The possibility that these improvements might delay joint replacements and other hospitalizations, thereby substantially offsetting some direct costs in the long term, has been discussed[4-8]. Also, it is plausible that short-term benefits of treatment on productivity as found in our study will be complemented with the longterm effects of treatment, such as reducing early retirement and keeping people in continuous employment[38]. Consequently, with further research on both the direct benefits and the potential longer term effects of treatment, the justification for funding biologic DMARD could be further strengthened.

We relied on the HLQ instrument to measure changes in productivity outcomes. Although the HLQ is one of the most validated and frequently used productivity instruments, there is debate regarding the manner in which patients should be asked the questions — mostly regarding how to quantify presenteeism estimates. The HLQ measures reduced productivity by asking patients to estimate the number of hours required to compensate for reduced work productivity rather than estimate reduced productivity directly[39]. Therefore, our estimate of reduced productivity (presenteeism) might be significantly lower than if we had used other instruments such as the Quantity and Quality instrument[39-41].

Our analysis was conducted from a societal perspective in which the costs of the drug and costs of productivity are seen equally as costs to society. However, it is likely that these costs influence different budgets, so costs offset might not be borne by the budget that paid for the drug. For example, for those patients with improved productivity, the drug cost may be assumed by patients themselves, insurance companies, government, or employers. However, only the employers and patients would directly benefit from the improved productivity.

The major limitation of our study is that we did not have a control arm (nonbiologic) with which to compare the productivity outcomes and costs. It is likely that regression to the mean plays an important role because patients with moderate to severe RA were included in this study. Further, the HLQ questionnaire assesses work productivity in the previous 2 weeks, and without a control group, we have insufficient insight on the natural fluctuations of worker participation over time. Therefore, the mean improvements and reductions in costs reported in Table 2 could be the result of a number of other factors, such as an upturn in employment opportunities or seasonal factors and differences in patients' baseline clinical characteristics. We therefore compared patients who responded to treatment with those who did not, adjusting for all measured potential confounders that were available. Our results found that response was a significant factor contributing to the reduction in total costs of productivity losses. Our post-hoc analysis comparing clinical responders with nonresponders is an attempt to account for the deficiency in design. However, given the design of the study, the issue of regression to the mean cannot be completely excluded.

Three additional limitations are worthy of further comment. First, there is disagreement over whether the human capital (HC) approach or the alternative friction cost (FC) method provides more accurate estimates of productivity losses. The FC approach assumes that employees who are absent from work as a consequence of a disease could be replaced after a (friction) period of adjustment[42]. If the absent workdays exceed the friction period, the friction peri-

od instead of the actual absent days will be used to estimate the productivity losses. The FC approach is also applied when measuring costs of presenteeism. For example, if making up for reduced performance (presenteeism) requires working overtime by a coworker, the loss in leisure time of the coworker should be valued[43]. It has been shown that the productivity costs estimated by HC substantially exceed those using FC, especially in the case of longterm disability and mortality[30,43], and the differences in estimates of the indirect costs between the FC method and the HC method will extend as time absent increases[42]. However, because our entire study period was only 12 weeks, this argument would not appear to be an issue with our study, as any friction period (e.g., 123 days used in HLQ manual[29]) would be longer.

Second, measuring work productivity using self-report questionnaires can be difficult because patients often are concerned that employers might see the results and make judgments based on them. It therefore remains a possibility that patients would exaggerate more productivity than less. There are few alternatives to this approach, and we ensured that patients included in the study knew that the data would remain confidential. Also, a 2-week recall period was used to measure productivity losses in an attempt to minimize the potential effect of recall bias especially on presenteeism.

Third, the CanAct trial was attempting to include those patients representative of the patients with moderately or severely active RA who have failed prior DMARD and who are eligible for treatment in Canadian clinical practices. However, as for any clinical study, the inclusion criteria and exclusion criteria might limit the generalizability of the study result and thus the absolute gains may not be generalized to reflect the true effects.

This is the first study to comprehensively examine work productivity outcomes among patients with RA receiving a biologic DMARD. Even in the short term, these new therapies appear to improve outcomes and offset costs because they induced clinical response. Further studies should be conducted to examine the longer term effects of therapies on productivity outcomes. Only 36% of our patients were in paid employment at baseline, and it remains to be proven whether biologic DMARD can help patients return to employment. Future studies should also examine presenteeism as well as absenteeism, as this appears to be an important component to productivity outcomes.

APPENDIX

Productivity Outcomes	Explanations	Sources
Primary Outcomes		
Absenteeism: no. of absent workdays	Calculated by counting the number of days that patients were unable to perform paid work due to health problems	HLQ: module 1
Presenteeism: no. of extra hours needed to work	Generated from the question, "How many extra hours would you have to work to catch up on tasks you were unable to complete in normal working hours due to health problems?"	HLQ: module 2
Unpaid work productivity: no. of hours of paid or unpaid help	The numbers of hours patients needed paid or unpaid labor to take over the household tasks (cleaning the house, shopping, taking care of children) were summed and then multiplied by 2 to obtain 2-week numbers	HLQ: module 3
Other Outcomes		
Indicator for impediments at paid work	Derived from the question, "Were you hindered by health problems at your paid work over the past 2 weeks?", with 3 options, "No, not at all," "Yes, to a degree," and "Yes, very much"	HLQ: module 2
Efficiency score	Measuring the influence of health problems on concentration, working pace, need to be alone, decision-making, postponement of work and taking over work by other workers. The unweighted scores were Never = 1, Sometimes = 2, Often = 3, Always = 4. Total score ranged from 6 to 24	HLQ: module 2
No. of hours spent on unpaid work	Four types of productive activities were distinguished for unpaid work: household work, shopping, odd jobs and chores, and childcare. The numbers of hours per week a patient spent on these activities were summed and then multiplied by 2 to obtain 2-week numbers	HLQ: module 3
Impediment score at unpaid work	A measure of difficulties experienced during unpaid work due to health problems. Respondents were asked whether they had performed each of the 4 unpaid activities in the past 2 weeks. "Did do" was followed by a question about the amount of trouble experienced as a result of health problems. "Did not do" was followed by question of to what extent this was caused by health problems. The scores for impediments at unpaid work were: Did do, hindered = 1; Did do, not hindered = 0; Did not do, due to health problems = 2; Did not do, due to other reasons = 0. The aggregated impediment score resulted after adding the items. The minimum score per item was 0 and the maximum 2. Total score had a range of 0 to 8	HLQ: module 4
Costs of Lost Productivity		
Cost of absenteeism	No. of absent workdays × daily wage	HLQ and CANSIM
Cost of presenteeism	No. of extra hours needed to work × hourly wage	HLQ and CANSIM
Cost of unpaid work	(No. of hours of unpaid help + no. of hours of paid help) × hourly wage for childcare and home support workers	HLQ and CANSIM
Total costs of lost productivity	Sum of the cost of absenteeism, cost of presenteeism, and cost of unpaid work	

HLQ: Health and Labour Questionnaire[29]; CANSIM: Canadian Socioeconomic Information Management Database[35].

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