

Original article

Estimated medical expenditure and risk of job loss among rheumatoid arthritis patients undergoing tofacitinib treatment: *post hoc* analyses of two randomized clinical trials

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Abstract

Objectives. RA causes high disability levels and reduces health-related quality of life, triggering increased costs and risk of unemployment. Tofacitinib is an oral Janus kinase inhibitor for the treatment of RA. These *post hoc* analyses of phase 3 data aimed to assess monthly medical expenditure (MME) and risk of job loss for tofacitinib treatment vs placebo.

Methods. Data analysed were from two randomized phase 3 studies of RA patients (n=1115) with inadequate response to MTX or TNF inhibitors (TNFi) receiving tofacitinib 5 or 10 mg twice daily, adalimumab (one study only) or placebo, in combination with MTX. Short Form 36 version 2 Health Survey physical and mental component summary scores were translated into predicted MME via an algorithm and concurrent inability to work and job loss risks at 6, 12 and 24 months, using Medical Outcomes Study data.

Results. MME reduction by month 3 was \$100 greater for tofacitinib- than placebo-treated TNFi inadequate responders (P < 0.001); >20 and 6% reductions from baseline, respectively. By month 3 of tofacitinib treatment, the odds of inability to work decreased $\geq 16\%$, and risk of future job loss decreased $\sim 20\%$ (P < 0.001 vs placebo). MME reduction by month 3 was \$70 greater for tofacitinib- than placebo-treated MTX inadequate responders (P < 0.001); ≥ 23 and 13% reductions from baseline, respectively. By month 3 of tofacitinib treatment, the odds of inability to work decreased $\geq 31\%$ and risk of future job loss decreased $\geq 25\%$ (P < 0.001 vs placebo).

Conclusion. Tofacitinib treatment had a positive impact on estimated medical expenditure and risk of job loss for RA patients with inadequate response to MTX or TNFi.

Key words: rheumatoid arthritis, biologic therapy, tofacitinib, economic outcomes, work outcomes, TNF inhibitors, health-related quality of life, expenditure, SF-36

Rheumatology key messages

- RA has significant impacts on health-related quality of life, particularly job loss, as well as medical expenditure.
- Tofacitinib treatment in RA may be associated with meaningful improvements in risk of job loss.
- Tofacitinib treatment may be associated with reductions in estimated medical expenditure for patients with RA.

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Introduction

Clinical studies have confirmed that RA treatment with DMARDs results in meaningful improvements in physical function and overall health-related quality of life (HRQL)

[1–10]. Improvements in these outcomes confer a reduction in disease-related costs to the individual and from a societal perspective [11]. These costs are often grouped into the following three main categories: direct costs, those associated with medical care or treatment of the disease; indirect costs, those associated with paid and unpaid activities (e.g. employment, schooling); and intangible costs, those associated with multiple domains of HRQL. Unlike HRQL, direct and indirect costs are not frequently measured in RA clinical trials. Nevertheless, there is growing interest in the overall impact of therapies on financial and well-being patient outcomes, as well as clinical ones.

Studies have shown that the high level of disability caused by RA significantly increases the risk of unemployment [12]. In a large longitudinal US study, ~25% of patients left employment or retired early because of RA within 6 years of diagnosis [13]. Other studies have reported that between one-third and one-half of patients become unable to work within 10 years of disease onset [14, 15], whereas Quinn *et al.* [16] found that ~20% of working patients with early RA experienced job loss within 1 year of conventional DMARD treatment, despite good clinical response. Attempts to estimate the impact of biologic agents on employment status have not always provided evidence of a positive effect; however, results have tended to favour biologic therapy over traditional DMARDs. An observational cohort study found no association between biologic therapy and Social Security disability, based on 4155 patients with RA with ≤5.5 years follow-up [17], whereas Yelin *et al.* [18] reported a 20% higher employment rate among etanercept-treated patients with long-standing RA compared with etanercept-naïve patients. Similar findings have been observed among patients with early RA, where a smaller percentage of patients became unemployable within a 2-year period with infliximab plus MTX treatment than with placebo plus MTX treatment (8 vs 14%, respectively; $P=0.05$) [19]. Finally, treatment with adalimumab has also been associated with a 10% lower rate of lost work days vs placebo (number of days absent as a proportion of the total number of working days; 18.4% for placebo vs 8.6% for adalimumab, $P=0.038$) [20]. These results show that it is important to evaluate changes in the likelihood of job loss to understand the impact of RA treatment.

Total medical expenditure associated with RA is also known to be high. An analysis of US administrative health-care and payroll data (2001–10) indicated that the average annual medical and prescription drug costs of employees with RA were \$4687 greater than for employees without RA ($P < 0.0001$) [21]. Despite the availability of evidence from analyses of claims data and other observational studies, medical expenditure data are not often estimated longitudinally in the context of clinical trials. Thus, as is the case with work-related outcomes, there remains a need to complement data from clinical trials with estimates of the impact of treatment on the economic burden of RA.

Tofacitinib is an oral Janus kinase inhibitor for the treatment of RA. Tofacitinib has demonstrated significant improvements in efficacy for clinical and HRQL outcomes during phase 2 [1, 9, 10, 22–24] and phase 3 [2–5, 25–27] clinical trials in patients with RA with an inadequate response to conventional DMARDs and TNF inhibitors (TNFi).

This analysis used the methodological approach previously reported by Cole *et al.* [28] to translate tofacitinib-related changes in Short Form 36 version 2 Health Survey (SF-36v2) scores into changes in estimated medical expenditure and risk of job loss.

Methods

Tofacitinib samples

Data from two phase 3 clinical trials were used in the current analysis. The design and primary results of both studies have been previously published [2, 5].

Briefly, ORAL Step [2] was a 6-month, double-blind study to evaluate the efficacy and safety of two doses of tofacitinib in patients with RA with inadequate response to TNFi. Patients ($n=399$) were randomized 2:2:1:1 to the following treatments: tofacitinib 5 mg twice daily (BID); tofacitinib 10 mg BID; placebo for 3 months, followed by tofacitinib 5 mg BID; or placebo for 3 months, followed by tofacitinib 10 mg BID. All patients received background MTX.

ORAL Standard [5] was a 1-year, double-blind, active-comparator study to evaluate the efficacy and safety of two doses of tofacitinib in patients with RA with inadequate response to stable MTX therapy. Patients ($n=716$) were randomized 4:4:1:1:4 to the following treatments: tofacitinib 5 mg BID; tofacitinib 10 mg BID; placebo followed by tofacitinib 5 mg BID; placebo followed by tofacitinib 10 mg BID; or adalimumab 40 mg s.c. once every 2 weeks. Patients randomized to placebo with no response (<20% improvement in tender/painful and swollen joint counts) by month 3 were advanced (blinded) to their randomized tofacitinib treatment. At the end of month 6, all patients originally randomized to placebo advanced (blinded) to their second predetermined treatment for the remainder of the study.

ORAL Step (Pfizer protocol A3921032; NCT00960440) and ORAL Standard (Pfizer protocol A3921064; NCT00853385) were approved by institutional review boards and independent ethics committees, and were carried out in accordance with the Declaration of Helsinki. Study participants provided written informed consent prior to randomization. The present *post hoc* analysis used data collected during these trials and therefore did not require further ethical approval.

The SF-36v2 health survey

The SF-36v2 is a 36-item, self-report survey of functional health and well-being [29]. Responses to 35 of the 36 items afford computation of an eight-domain profile of functional health and well-being scores, with higher values indicating better HRQL. Factor analyses of

correlations among these eight health-domain scales have consistently identified two factors. Based on the strength of the pattern of their correlations with the eight scales, they are interpreted as the physical component summary (PCS) and mental component summary (MCS) of health status. PCS and MCS are computed by first scoring the eight scales according to the standard SF-36v2 scoring algorithms [29], then multiplying each SF-36v2 scale score by its respective physical or mental factor score coefficient and summing the eight products.

Medical expenditure

Calculation of monthly medical expenditure (MME) was based on the algorithm of Fleishman *et al.* [30]. The algorithm traditionally uses SF-12v2 scores (a shorter version of SF-36v2), rather than the SF-36v2 scores used in the present analysis; however, given the strong correlation between SF-12v2 and SF-36v2 scores for both PCS and MCS ($r \geq 0.94$ for both [31, 32]), any differences associated with using the SF-36v2 PCS and MCS scores, instead of those from the SF-12v2, should be negligible. Calculation of predicted per-patient MME using the algorithm accounts for the patient's age, gender and SF-12v2 or SF-36v2 component summary scores. The algorithm was developed by testing a series of regression models of increasing complexity using the 2000–01 Medical Expenditure Panel Survey (MEPS) data from a sample of the US general population ($n=5542$). The authors evaluated goodness of fit by examining residuals across the distribution of predicted expenditures, the modified Hosmer–Lemeshow and Pregibon's goodness-of-fit tests and by flagging influential observations through Cooks' D statistic. The final models were obtained after extensive testing for potential non-linearity between the predictors and expenditures. The cost sources used in calculating MME refer to direct payments for care, including out-of-pocket expenses and payments made by private insurance companies, Medicaid, Medicare and other sources for non-institutionalized persons. Types of medical expenditure included costs of prescription medications, inpatient hospital stays, home health visits, medical supplies and visits to various health-care providers (including dentists). Over-the-counter medications and most alternative care expenses are not included in the calculated MME. MME based on the MEPS data driving these algorithms did not consider expenditures specifically related to biologic treatment nor did the algorithm differentiate between patients on biologic treatment vs those who were not. A more recent study using a similar analytical approach has confirmed these results specifically in MEPS participants identified as having arthritis [33].

Job loss and inability to work

The Medical Outcomes Study (MOS) [34] showed the relationship between SF-36 PCS and MCS and the following: concurrent inability to work; job loss at 6 months; job loss at 1 year; and job loss at 2 years. Briefly, the MOS was a large ($n > 23\,000$), 4-year, longitudinal observational study of the variations in practice styles and health

outcomes for chronically ill patients. Data from the MOS have been used to link baseline SF-36v2 scores to various major life events, including mortality and hospitalization, in addition to job loss [29]. Linearity between SF-36v2 scores and work-related outcomes was verified by examining separate regression coefficients across percentiles of the predictive score and by performing linear-by-linear association tests [35]. Summary statistics for variables from the MOS database used to derive the relationship between PCS and MCS and each of the four work-related outcomes in the two clinical trial data sets have been previously presented [28]. In summary, 25% of patients were unable to work at the time of the MOS survey, and job loss at 6, 12 and 24 months was reported by 11, 15 and 16% of respondents, respectively. Data from these patients were used in logistic regression models to calculate estimates of the log-odds of each outcome as a function of PCS and MCS scores at baseline. These coefficients were then applied to the two clinical trial data sets to estimate the corresponding odds ratio (OR). For work-related outcomes, only patients 65 years of age or younger were included in the analyses.

Statistical analysis

Analysis of variance with Turkey–Kramer adjustment for multiple comparisons was conducted to test the significance of baseline differences in PCS, MCS, MME and age between treatment groups. Differences in gender distribution were assessed using the χ^2 test. Non-parametric tests were also used to test differences between treatment groups to examine the consistency of results in the case of skewed distributions. Fit statistics (Akaike information criterion and Bayesian information criterion) indicated that an unstructured covariance best described the correlation between repeated measures on the same patient. An examination of studentized residuals from the regression models indicated no marked violations of model assumptions.

Logistic regression analysis was used to estimate the effect of SF-36v2 PCS and MCS scores on each of the outcomes, controlling for age and gender. The logistic regression coefficients translate into the OR of the outcome as a function of a one unit difference in PCS or MCS scores. The OR corresponding to a difference of x units can then be obtained by raising its value to the power x (i.e. OR^x). Centering of PCS and MCS scores on a reference value provides a direct interpretation of the OR as the odds of the outcome at the observed PCS or MCS score relative to the reference value. Unlike the study by Cole *et al.* [28], where the reference values were taken to be the PCS and MCS means of the US general population (50, in both cases), in the present study the baseline PCS and MCS scores of each individual patient were used as reference, such that the baseline OR equalled one for each patient. Thus, at each time point an estimate of the change in the odds of the outcome relative to each individual's odds at baseline was obtained.

Differences in the estimated ORs across treatment groups were tested using the following repeated

measures model:

$$OR_{ijk} = \beta_0 + \beta_1 \times \text{Time}_i + \beta_2 \times \text{Treatment}_j + \beta_3 \times \text{Time}_i \times \text{Treatment}_j + \epsilon_{ijk}$$

where OR_{ijk} represents the estimated OR of patient k , in treatment j at time i . Given that this OR was calculated as a function of the individual baseline score, only post-baseline data were included in these models.

Differences across treatment groups in estimated MME were evaluated using the following longitudinal model:

$$MME_{ijk} = \beta_0 + \beta_1 \times \text{Time}_i + \beta_2 \times \text{Treatment}_j + \beta_3 \times \text{Time}_i \times \text{Treatment}_j + MME_{\text{baseline}} + \epsilon_{ijk}$$

where MME_{ijk} represents the MME of patient k , in treatment j at time i .

In each case, the following three variance-covariance structures were used in alternative models: unstructured; auto-regressive of order 1; and compound symmetry. The final variance-covariance structure was selected based on Akaike's information criteria. Studentized residuals were examined for the final model to examine potential violations of model assumptions and/or unusual observations that could unduly influence the results. All P-values from pairwise tests were evaluated after applying Bonferroni and Sidak adjustments for multiple comparisons.

Although statistical summaries for ORAL Step are presented for all four treatment groups until month 6, only data from the first 3 months, representing measurements before changes in treatment regimen, were included in testing of treatment group differences. Likewise, for ORAL Standard, only data from the first 3 months, before changes in treatment regimen, were included in testing of treatment group differences. This approach ensured a large enough sample size within each treatment group to allow for more robust testing of effects, and enabled visualization of changes that occurred after the switch to active treatment in ORAL Step. Given that in ORAL Standard the patients switched from placebo to tofacitinib at different time points, starting at month 3,

longitudinal summaries of treatment groups are not presented beyond that time.

The analyses were not designed to detect differences between tofacitinib and adalimumab.

Results

Baseline scores

Data from 399 patients from ORAL Step and 716 patients from ORAL Standard were included in this analysis. Table 1 shows the key variables used in the analyses: age and gender, as well as mean (s.d.) PCS, MCS and MME. As previously reported [5], ORAL Standard patients were primarily white (range, 67.3–74.0%) and had a mean duration of RA that ranged from 6.9 to 9.0 years across treatment groups. TNFi inadequate responders in ORAL Step had longer mean disease duration (11.3–13.0 years across treatment groups), and were also primarily white (range 81.2–84.8%) [2].

Differences in estimated medical expenditures across treatment groups

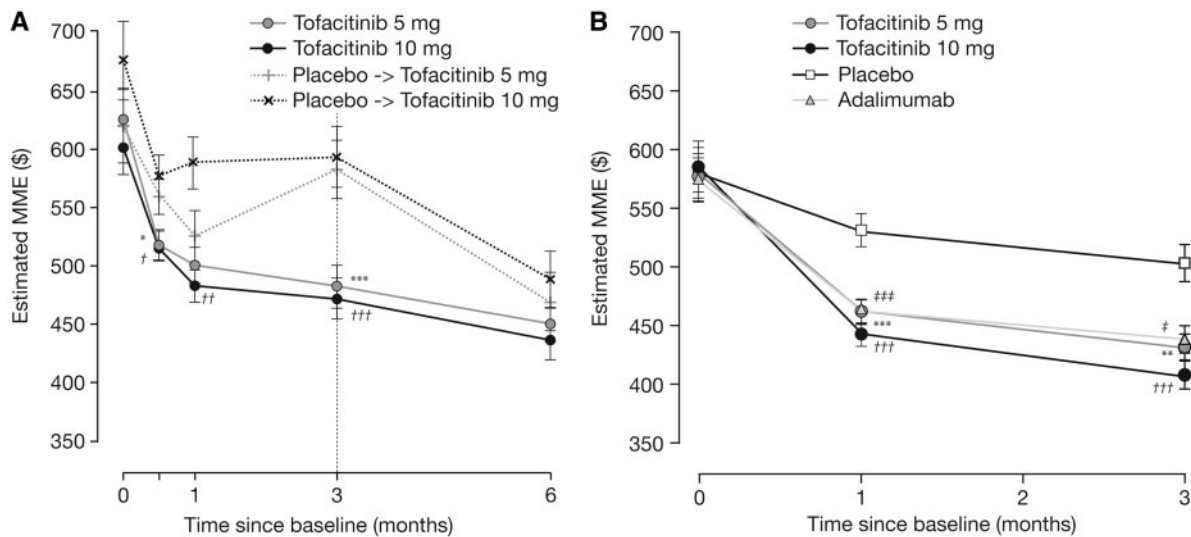
Among TNFi inadequate responders, statistically significant differences compared with placebo in MME were observed for tofacitinib 10 mg BID and tofacitinib 5 mg BID as early as 2 weeks into treatment ($F=5.43$; $P=0.005$; Fig. 1A). At month 1, only patients receiving tofacitinib 10 mg BID had a significantly lower mean MME than placebo-treated patients (tofacitinib 10 mg: $MME = -\$72$, $P=0.006$; tofacitinib 5 mg: $MME = -\$55$, $P=0.084$), but by month 3 both active treatment groups had significantly lower MME values than placebo (tofacitinib 10 mg: $MME = -\$115$, $P < 0.001$; tofacitinib 5 mg: $MME = -\$104$, $P < 0.001$). Although all groups demonstrated a statistically significant decrease in MME from baseline to month 1 and for tofacitinib-treated patients it continued to decrease, by month 3 the mean MME of placebo-treated patients increased (+\$100, 20% greater). Estimates of within-group change indicated a 23% decrease in MME for tofacitinib-treated patients, whereas placebo-treated patients had a ~6% decrease.

TABLE 1 Baseline comparisons of key analysis variables across treatment groups

Variable	ORAL Step TNFi inadequate responders (n = 399)			ORAL Standard MTX inadequate responders (n = 716)			
	Tofacitinib 5 mg BID (n = 133)	Tofacitinib 10 mg BID (n = 134)	Placebo (n = 132)	Tofacitinib 5 mg BID (n = 204)	Tofacitinib 10 mg BID (n = 201)	Placebo (n = 107)	Adalimumab 40 mg Q2W (n = 204)
Age, mean (s.d.), years	55.4 (11.5)	55.1 (11.3)	54.4 (11.3)	53.0 (11.9)	52.9 (11.8)	53.8 (13.8)	52.5 (11.7)
Gender, female, n (%)	113 (85.0)	116 (86.6)	106 (80.3)	174 (85.3)	168 (83.6)	81 (75.7)	162 (79.4)
PCS ^a score, mean (s.d.)	30.7 (9.3)	32.1 (7.6)	30.0 (8.0)	33.1 (7.7)	32.7 (7.8)	33.0 (6.2)	32.7 (6.9)
MCS score, mean (s.d.)	42.8 (12.7)	43.2 (12.8)	41.3 (13.3)	39.8 (11.6)	40.2 (11.1)	43.3 (10.5)	40.6 (11.6)
MME, mean (s.d.)	625.1 (284.1)	601.2 (269.4)	647.3 (263.8)	578.2 (248.3)	582.7 (249.1)	581.2 (309.5)	575.3 (271.9)

^aKruskal-Wallis test: $\chi^2=6.47$; $P=0.039$. BID: twice daily; MCS: mental component summary; MME: monthly medical expenditure; PCS: physical component summary; Q2W: once every 2 weeks; TNFi: TNF inhibitor.

Fig. 1 Estimated monthly medical expenditure for TNF inhibitor inadequate responders (A) and MTX inadequate responders (B)



(A) Mean (s.e.m.) MME for TNF inhibitor inadequate responders from ORAL Step. Tofacitinib 5 mg BID and 10 mg BID vs combined placebo groups. Placebo data are from before the month 3 advance to active treatment, indicated by the dotted line. (B) Mean (s.e.m.) MME for MTX inadequate responders from ORAL Standard. Tofacitinib 5 mg BID and 10 mg BID and adalimumab 40 mg Q2W vs combined placebo groups. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ 5 mg vs placebo; † $P < 0.05$, †† $P < 0.01$, ††† $P < 0.001$ 10 mg vs placebo; ‡ $P < 0.05$, ‡‡ $P < 0.01$, ‡‡‡ $P < 0.001$ adalimumab vs placebo. BID: twice daily; MME: monthly medical expenditure; Q2W: once every 2 weeks.

Patients who had been on placebo until month 3 experienced a decrease in MME by month 6 following the switch to active treatment.

After 1 month of tofacitinib 10 mg BID, MTX inadequate responders had a mean MME \$89 less than those treated with placebo ($P < 0.001$; Fig. 1B). Likewise, after 1 month of treatment, the mean MME of patients receiving tofacitinib 5 mg BID or adalimumab was \$70 less than patients receiving placebo ($P \leq 0.001$ for both). These differences remained until month 3, and by that time the decrease in MME was ~29, 25 and 24% from baseline for the tofacitinib 10 mg BID, tofacitinib 5 mg BID and adalimumab groups, respectively, whereas for the placebo group the decrease was ~13%. At month 3, relative to placebo, tofacitinib 10 mg BID showed the largest difference ($-\$95.1$, $P < 0.001$) in mean MME, followed by tofacitinib 5 mg BID ($-\$70.8$, $P = 0.004$) and adalimumab ($-\$64.9$, $P = 0.012$).

Differences in estimated odds of work-related outcomes across treatment groups

Table 2 presents the mean ORs for work-related outcomes for each treatment group based on PCS scores for TNFi and MTX inadequate responders. In both samples, the estimated ORs were significantly different at month 3, with a decrease in the odds of each outcome for actively treated patients but not for placebo-treated patients. By month 3, the odds of being unable to work for the TNFi inadequate responder sample increased by

17% for placebo-treated patients and decreased by between 19 and 23% for tofacitinib 5 mg BID and 10 mg BID groups, respectively. Likewise, while patients in the placebo group experienced no change in their risk of future job loss, the odds of job loss for those receiving active treatment decreased ~20% ($P \leq 0.01$ tofacitinib vs placebo).

Results were similar for the MTX inadequate responder sample. The ORs for placebo-treated patients remained close to 1 at month 3, with 15% increase in odds of concurrent inability to work and 3% decrease in odds of future job loss. Tofacitinib-treated patients had a 30 and 41% mean decrease in odds of concurrent inability to work in the 5 and 10 mg arms, respectively. The odds of being unable to work at months 6, 12 and 24 were ~25% for the tofacitinib 5 mg BID group and 30% for the tofacitinib 10 mg BID group ($P \leq 0.0001$, both groups vs placebo). Adalimumab-treated patients also experienced odds reductions for concurrent inability to work and future job loss, between 21 and 22% ($P \leq 0.01$ vs placebo).

Table 3 presents the mean ORs for work-related outcomes based on MCS scores of treatment groups for TNFi and MTX inadequate responders. At month 3, MCS-based ORs remained close to the baseline value of 1 for actively treated patients, with mean decreases in outcome odds not exceeding 10% across the four outcomes in the TNFi inadequate responder sample and not exceeding 13% (tofacitinib 10 mg BID group) in the MTX inadequate responder sample. For both samples, the

TABLE 2 Month 3 odds ratios for work-related events based on physical component summary scores

Treatment group	Inability to work	Job loss at month 6	Job loss at month 12	Job loss at month 24
ORAL Step TNFi inadequate responders^a	Mean OR (95% CI)	Mean OR (95% CI)	Mean OR (95% CI)	Mean OR (95% CI)
Tofacitinib 5 mg BID	0.81** (0.61, 1.00)	0.77*** (0.68, 0.87)	0.78** (0.68, 0.87)	0.78** (0.69, 0.87)
Tofacitinib 10 mg BID	0.77*** (0.58, 0.96)	0.78*** (0.69, 0.87)	0.77*** (0.69, 0.87)	0.78*** (0.70, 0.87)
Placebo	1.17 (0.97, 1.36)	1.01 (0.91, 1.10)	1.01 (0.91, 1.10)	1.00 (0.91, 1.08)
F	4.99	7.59	7.59	7.83
P-value	0.007	<0.001	<0.001	<0.001
ORAL Standard MTX inadequate responders^b				
Tofacitinib 5 mg BID	0.70** (0.55, 0.85)	0.74*** (0.68, 0.81)	0.74*** (0.68, 0.81)	0.75*** (0.69, 0.81)
Tofacitinib 10 mg BID	0.59*** (0.44, 0.75)	0.68*** [†] (0.61, 0.75)	0.68*** [†] (0.61, 0.75)	0.69*** [†] (0.63, 0.76)
Placebo	1.15 (0.93, 1.36)	0.97 (0.87, 1.06)	0.97 (0.87, 1.06)	0.96 (0.87, 1.05)
Adalimumab 40 mg Q2W	0.79** (0.64, 0.94)	0.78** (0.72, 0.85)	0.78** (0.72, 0.85)	0.79** (0.73, 0.85)
F	5.87	7.92	7.92	8.07
P-value	<0.001	<0.0001	<0.0001	<0.0001

Month 3 odds ratios for work-related events are based on physical component summary scores of the Short Form 36 version 2 Health Survey. ^aPatient sample of 592 patients (83% of initial sample). ^bPatient sample of 319 patients (80% of initial sample). *** $P \leq 0.001$, ** $P \leq 0.01$ vs placebo; [†] $P \leq 0.05$ vs adalimumab. BID: twice daily; OR: odds ratio; Q2W: once every 2 weeks; TNFi: TNF inhibitor.

TABLE 3 Month 3 odds ratios of work-related events based on mental component summary scores

Treatment group	Inability to work	Job loss at 6 months	Job loss at 12 months	Job loss at 24 months
ORAL Step TNFi inadequate responders	Mean OR (95% CI)	Mean OR (95% CI)	Mean OR (95% CI)	Mean OR (95% CI)
Tofacitinib 5 mg BID	0.93 (0.79, 1.08)	0.92* (0.81, 1.03)	0.92* (0.82, 1.01)	0.92* (0.83, 1.00)
Tofacitinib 10 mg BID	0.91* (0.77, 1.05)	0.90* (0.80, 1.01)	0.90* (0.81, 1.00)	0.91* (0.82, 0.99)
Placebo	1.13 (0.99, 1.27)	1.07 (0.96, 1.17)	1.05 (0.96, 1.15)	1.04 (0.96, 1.13)
F	2.82	2.97	3.00	3.04
P-value	0.061	0.053	0.051	0.049
ORAL Standard MTX inadequate responders				
Tofacitinib 5 mg BID	0.98* (0.88, 1.08)	0.96* (0.88, 1.04)	0.96* (0.89, 1.03)	0.96* (0.89, 1.02)
Tofacitinib 10 mg BID	0.86*** (0.76, 0.96)	0.86*** (0.79, 0.94)	0.87*** (0.80, 0.94)	0.87*** (0.81, 0.93)
Placebo	1.19 (1.04, 1.33)	1.11 (1.00, 1.22)	1.09 (1.00, 1.19)	1.08 (0.99, 1.17)
Adalimumab 40 mg Q2W	0.98* (0.89, 1.08)	0.96* (0.89, 1.04)	0.96* (0.89, 1.02)	0.95* (0.89, 1.02)
F	4.49	4.64	4.69	4.72
P-value	0.004	0.003	0.003	0.003

Month 3 odds ratios for work-related events are based on mental component summary scores of the Short Form 36 version 2 Health Survey. No significant differences were observed between tofacitinib and adalimumab. *** $P \leq 0.001$, [†] $P \leq 0.05$ vs placebo. BID: twice daily; OR: odds ratio; Q2W: once every 2 weeks; TNFi: TNF inhibitor.

estimated MCS-based ORs for placebo-treated patients indicated that these patients had a slightly increased likelihood of concurrent inability to work and future job loss, ranging between 4 and 19%. Although F-tests indicated significant differences between treatment groups at month 3, these were generally related to modest reductions in the likelihood of job loss, with the exception of the tofacitinib 10 mg BID group, which experienced a greater average decline in risk of job loss and inability to work,

including significantly lower odds of each outcome compared with placebo ($P < 0.001$).

Discussion

The results of this study suggest that improvements in HRQL related to tofacitinib treatment are likely to translate into significant reductions in medical expenditure and likelihood of job loss (current and future), both of which

are essential metrics for understanding the overall effectiveness of therapy. Although generally small and failing to achieve statistical significance, between-group differences suggested slightly larger gains in these outcomes for patients receiving tofacitinib 10 mg BID compared with adalimumab. Consistent with results of an earlier study [28], where the impact of abatacept on medical expenditure and likelihood of job loss was examined using the same approach, differences between placebo and tofacitinib were generally higher among TNFi inadequate responders than MTX inadequate responders. Also similar to the previous study, PCS proved to be a better indicator of treatment-related reductions in the likelihood of job loss than MCS. This is also consistent with an analysis of data from seven RA clinical trials, which indicated that the effect size of the SF-36v2 MCS was small (0.21) and only half the PCS effect size (0.42) [36]. Furthermore, our results are also consistent with those from a systematic review [37] examining the effect of biologic agents on work outcomes, which indicated that employment status was improved in 4 out of 13 studies, and absence from work in all 10 studies.

The present study is limited because the outcomes analysed were modelled rather than directly measured. Data from large non-clinical studies, powered on ACR, were used to estimate links between disease-related outcomes and the physical and mental functioning of patients, as measured by the SF-36v2. Although the tests of statistical significance presented in the present study reflect variability in the data from the tofacitinib trials, they do not incorporate the uncertainty present in the predictive algorithms. Although this is in agreement with Cole *et al.* [28], future studies should address this limitation. Furthermore, summary statistics used to derive the relationship between HRQL and work-related outcomes were based on the MOS study of chronically ill patients, so were not specific to patients with RA. Another limitation was that the MEPS claims data used to derive the MME estimates were collected ~10 years before this analysis, and availability costs and patterns of RA treatments are known to have changed significantly since then. Therefore, estimated reductions in MME were also analysed as the percentage change in MME since baseline, to aid in the interpretation of results. Furthermore, it is expected that the treatment- and control-group data were affected in a similar manner, and therefore little or no effect on analyses of treatment group differences would have been observed.

Despite their recognized importance, data quantifying the effect of biologic RA treatment on work-related events and medical expenditure continue to be scarce. The impact of biologic therapy has been studied in a retrospective observational study of etanercept treatment in all stages of RA [18], in the secondary analysis of a 46-week efficacy study of infliximab [19] and in a placebo-controlled study of MTX-naïve patients undergoing adalimumab treatment [20]. Only the last of these studies was specifically designed to assess employment status outcomes related to treatment.

Results with active treatment from that study failed to reach statistical significance vs placebo for the job loss/imminent job loss end point at week 56, which may have been because of the considerable dropout rates observed. However, after week 56 there was significantly less job loss/imminent job loss in the adalimumab plus MTX group compared with the placebo plus MTX group ($P=0.005$) [20]. In the infliximab study, employment rates were not statistically different across treatment groups, but patients who were treated with MTX plus infliximab had a higher probability of maintaining employability and fewer lost work days compared with those who received MTX alone [19].

This study contributes to the body of research that has attempted to evaluate the association between different RA treatments and job loss and MME in the context of clinical trials, and suggests that, in addition to the demonstrable clinical efficacy, treatment with tofacitinib may be associated with meaningful improvements in these additional outcomes. Further studies directly measuring work-related outcomes would help to provide a better understanding of the full impact of RA treatment.

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