EXTENDED REPORT

Estimating the monetary value of the annual productivity gained in patients with early rheumatoid arthritis receiving etanercept plus methotrexate: interim results from the PRIZE study

Wei Zhang,[1,2] Nick Bansback,[1,2] Huiying Sun,[1] Ronald Pedersen,[3] Sameer Kotak,[3] Aslam H Anis[1,2]

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[1]Centre for Health Evaluation and Outcome Sciences, St Paul's Hospital, Vancouver, British Columbia, Canada
[2]School of Population and Public Health, University of British Columbia, Vancouver, British Columbia, Canada
[3]Pfizer Inc., Collegeville, Pennsylvania, USA

Correspondence to
Dr Aslam H Anis;
aslam.anis@ubc.ca

ABSTRACT

Objective: To measure and value the impact of combined etanercept (ETN) and methotrexate (MTX) therapy on work productivity in patients with early rheumatoid arthritis (RA) over 52 weeks.

Methods: MTX- and biological-naïve patients with RA (symptom onset ≤12 months; Disease Activity Score based on a 28-joint count (DAS28) >3.2) received open-label ETN50/MTX for 52 weeks. The Valuation of Lost Productivity (VOLP) questionnaire, measuring paid and unpaid work productivity impacts, was completed approximately every 13 weeks. Bootstrapping methods were used to test changes in VOLP outcomes over time. One-year productivity impacts were compared between responders (DAS28 ≤3.2) at week 13 and non-responders using zero-inflated models for time loss and two-part models for total costs of lost productivity.

Results: 196 patients were employed at baseline and had ≥1 follow-up with VOLP. Compared with baseline, at week 52, patients gained 33.4 h per 3 months in paid work and 4.2 h per week in unpaid work. Total monetary productivity gains were €1322 per 3 months. Over the 1-year period, responders gained paid (231 h) and unpaid work loss (122 h) compared with non-responders, which amounted to a gain of €3670 for responders.

Conclusions: This is the first clinical trial to measure and value the impact of biological treatment on all the labour input components that affect overall productivity. Combination therapy with ETN50/MTX was associated with a significant productivity gain for patients with early RA who were still observed at week 52. Over the 1-year treatment period, responders at week 13 suffered significantly less productivity loss than non-responders suggesting this gain was related to treatment response.

Trial registration number: ClinicalTrials.gov number NCT00913458

Key messages

What is already known about this subject?
▶ Rheumatoid arthritis (RA) has a substantial effect on work productivity in the very early phase of the disease.

What does this study add?
▶ This study measures how much productivity patients with early RA gain when on combination therapy with etanercept and methotrexate.

How might this impact on clinical practice?
▶ The combination therapy is associated with a significant productivity gain for patients who remained on treatment at week 52.
▶ Over a 1-year treatment period, early responders at week 13 had significant productivity gains compared with non-responders, which suggests this gain is related to treatment response.

INTRODUCTION

Rheumatoid arthritis (RA) is a systemic inflammatory disorder with an annual incidence of 3/10 000 adults.[1] It has been demonstrated that RA has a substantial effect on work productivity and the effect can occur at the very early phase of the disease. Using a multinational database, Sokka et al[2] found among 1756 patients whose symptoms had begun during the 2000s and who were working, 20% of them had stopped working at 2 years and 32% at 5 years. Furthermore, patients with recent-onset RA who are still in paid-employment often take sick leave. Merkesdal et al[3] reported an average of 82 days of sick leave per person-year within the first 3 years of RA. The ability to work is one of the most valued areas for patients with RA.[4] Developing effective treatments and strategies to improve patient work productivity in patients with early RA is therefore an important priority.

Recently, clinical trials have demonstrated that initial aggressive treatment of RA with a

combination of disease-modifying antirheumatic drugs (DMARDs) or early intervention with a combination of biological therapy with methotrexate (MTX) can reduce duration of sick leave and RA-related work disability.[5–7] However, these studies focused on measuring job loss and absent workdays, which provides only partial evidence of the effect of early intervention on overall productivity.

According to economic theory, production or output, is typically determined by three factors: capital input, labour input and technology.[8] Thus, productivity loss due to health problems is the output loss due to reduced labour input attributable to poor health. Productivity loss is typically measured according to time loss, that is, the time a person is not at a job (job loss/stopping work), absent from work (absenteeism), not working while at work (presenteeism), or unable to do unpaid work due to poor health. Productivity loss is then monetised into productivity costs by multiplying time loss by the wage rate and a multiplier that adjusts the wage rate to account for actual output loss due to reduced labour input.[8 9]

The objective of this study was to comprehensively evaluate the impact of open-label treatment with a combination of etanercept (ETN) and MTX on work productivity in patients with early active RA over 52 weeks. To the best of our knowledge, no studies have measured the impact when considering all the different types of labour input components that affect productivity and the corresponding monetary value among patients with early RA.[7 10] Thus, although it is well known that the short-term and long-term work disability are reduced in patients with early active RA receiving early intervention,[11–13] it is still unknown how much exactly overall productivity gains accrue to these patients.

METHODS
Study design
This study is based on phase 1 data from the PRIZE trial. The trial design included a three-phase study to evaluate the efficacy of combined ETN and MTX therapy in patients with early RA (phase 1) and to assess whether efficacy (remission) can be maintained with ETN dose reduction or biological-free (phase 2) or drug-free (phase 3).[14 15] The participants had symptom (swollen joints) onset ≤12 months from enrolment and active disease as indicated by a Disease Activity Score based on a 28-joint count (DAS28) >3.2. Phase 1 was a 52-week open-label, single-arm period in which all participants were treated with ETN50 mg once weekly plus MTX. Participants who were not in sustained remission or who did not have low disease activity (DAS28 >3.2) at the week 39 visit were withdrawn from the study and treated in accordance with local clinical practice.

Valuation of Lost Productivity (VOLP) questionnaire and outcomes
The Valuation of Lost Productivity (VOLP) questionnaire measures all the time input loss components (absenteeism, presenteeism, employment status changes, and unpaid work productivity loss) as well as information on job and workplace characteristics, based on which wage multipliers can be calculated to value the productivity loss attributable to reduced time input of workers.[9] The VOLP has been validated in patients with RA.[16]

In this study, the VOLP was measured approximately every 13 weeks. The main VOLP outcomes of interest at each administration were (1) paid work productivity loss (hours) in the past 3 months, the sum of hour loss from absenteeism, presenteeism and employment status changes; (2) unpaid work productivity loss (hours) in the past 7 days, quantified by the number of hours of getting help on unpaid work activities; (3) total costs of lost productivity in the past 3 months, the sum of the costs of paid and unpaid work productivity loss.

The main VOLP outcomes of interest during the 1-year study period were (4) paid work productivity loss (hours); (5) unpaid work productivity loss (hours); (6) total costs of lost productivity. These three outcomes were the sum of the corresponding outcomes at weeks 13, 26, 39 and 52. The Last Observation Carried Forward (LOCF) method was applied for any missing follow-up to calculate these outcomes. The main concern for this study is those patients who would be withdrawn from the trial if they did not achieve DAS28 ≤3.2 at week 39. The LOCF method underlies the assumption that these patients would not get the treatment and thus remain the same productivity level. As a sensitivity analysis, the missing data were also replaced by multiple imputations using the fully conditional specification method (the MI procedure in SAS 9.4, SAS Institute, Cary, North Carolina, USA).[17] The details on the outcome definitions and multiple imputation method can be found in the online supplementary appendix.

Costing of productivity loss
Since this trial was conducted in multiple countries, we cost the paid work loss by converting the patients self-reported income into Euros in 2010 using Purchasing Price Parties obtained from World Bank.[18] For unpaid work productivity loss, we used the 2010 hourly earnings (Euro) reported by the Eurostat for service and sales workers in each country.[19] The VOLP enables the calculation of wage multipliers for absenteeism and presenteeism based on the workplace characteristics (team work status, availability of substitutes and their substitutability).[9] Costs incorporating these multipliers represent productivity loss instead of wage loss and were calculated as 'lost time×wage×multiplier'. Costs with multipliers are presented in the paper, while costs without multipliers are in the online supplementary appendix.

Productivity loss versus productivity gain
Productivity loss is an outcome that is calculated at each time point and cumulatively at 1 year. A productivity gain is defined when comparing outcomes between time-points and different groups. For example, when

productivity loss at each time point decreased compared with baseline, the change in loss was defined as productivity gain over time. Moreover, when comparing productivity loss between responders and non-responders, if responders had reduced productivity loss in comparison to non-responders, this is referred to as a gain in productivity for responders.

Analyses

Our analysis focused on the participants who were employed at baseline and who had ≥1 follow-up with VOLP (weeks 13, 26, 39 and 52). The main VOLP outcomes of interest at week 52 were compared to those at baseline to assess the productivity gained in patients receiving the combination therapy. Since the protocol allowed some patients to discontinue at week 39, we also compared the VOLP outcomes at week 39 to those at baseline. For categorical variables, McNemar's test was used to examine percentage changes while the paired t test was used for the comparison of continuous variables. Since the continuous VOLP outcomes were highly skewed with inflated zeros, bootstrapping methods were used to test hypotheses.[20–22]

Patients were categorised into two groups, early responders versus non-responders, according to their disease activity at week 13 (DAS28 ≤3.2 vs DAS28 >3.2). Bootstrapping t test was used to test for differences in VOLP outcomes over 1 year across groups. Our analytical objective was to measure the association of early response status with 1 year productivity loss. To ensure an unbiased coefficient of response status variable, we also adjusted for potential confounders and the unbalanced characteristics between responders and non-responders at baseline. Based on previous review papers on the predictors/variables related to work disability in RA,[23 24] there was evidence showing sociodemographic variables, clinical variables and work-related factors were associated with work disability in RA. However, to avoid overadjustment and address the issue that some variables might be highly correlated (multicollinearity), we did not include all variables we measured at baseline in the final model. Details of the variable selection method can be found in the online supplementary appendix.

Since many patients had no productivity loss, we used zero-inflated negative binomial models (ZINB) to compare paid and unpaid work productivity loss (hours) during 1 year. For 1 year total costs of lost productivity, a two-part model (logistic regression for the probability of no costs and generalised linear model with γ distribution and log link for nonzero costs) was performed for the comparison.

Furthermore, to improve the interpretation of the coefficients of the ZINB and two-part models, we first computed the expected values for responders and non-responders, respectively, while holding the model covariates at their mean value. Then, we computed the difference in expected values between responders and non-responders, which we refer to as the marginal effects. Bootstrapping methodology was used to calculate the CIs.

RESULTS

Among the total of 306 patients participating in phase 1, 204 reported they were employed at baseline, 101 were unemployed and 1 patient's employment status was missing (figure 1). 196 employed patients who had ≥1 follow-up with VOLP were included in our final analysis. Among them, 154 completed the phase 1 and 42 did not, including 19 patients who were withdrawn due to not achieving low disease activity at week 39 and 23 patients who discontinued for reasons including adverse events, participant request, investigator judgment, protocol violation or sponsor's decision.

Average age of study participants was 46 years and 68% were women (table 1). About 62% were working full time and 11% did heavy work or carried very heavy loads. Average working time was 36.01 h or 4.87 days per week. The estimated wage multipliers implied that the productivity loss was 1.58 or 1.55 times more than the wage loss due to absenteeism and presenteeism, respectively. For example, a productivity loss due to a 1 h absence from work would be calculated to be 1.58 times the hourly wage of the patient.

Table 2 presents descriptive statistics of VOLP outcomes by visits. The bolded row shows the numbers of non-missing values used to generate the statistics for each outcome. Decreasing numbers of non-missing values were partially due to the missing responses and partially due to discontinuation. A small percentage of patients changed their employment status, for example, stopped working, due to their poor health. The percentage of patients who stopped work due to their health became smaller over the follow-ups and there were also a few patients who restarted working after their initial work stoppage. At baseline, about 58% of patients reported being absent from work over the past 3 months. On average, the absent hours were 75.7 h, which accounted for 17% of their usual working time. About 39% of patients reported that they would complete the same work in less time if they did not experience any health problems. The percentage of time loss while working due to health in the past 7 days was 8%.

Both absenteeism and presenteeism showed a declining trend over the 52-week follow-up. Overall, paid work loss was 111.7 h over the past 3 months at baseline, accounting for 25% of usual working time, and decreased to 60.1 h at week 52, which accounted for 13% of usual working time. Similarly, unpaid work loss was 6.3 h per week at baseline and declined to 1.8 h per week at week 52. Total costs of lost productivity over the past 3 months were €3483 at baseline and €843 at week 52. The reductions in these outcomes imply significant gains in paid and unpaid work productivity at week 52 (table 3). Patients gained 33.4 h per 3 months in paid work and 4.2 h per week in unpaid work. The total monetary gains in paid work and unpaid work were about €1322 per 3 months. Significant paid and unpaid work productivity gains were also observed at week 39.

Table 1 Baseline patient characteristics

Variable	N	Mean (SD) or N (%)
Demographics		
Age, years	196	46.43 (11.39)
Women	196	134 (68.4)
Body mass index	196	26.39 (4.89)
Smoking status		
Non-smoker	196	100 (51.0)
Has stopped	196	41 (20.9)
Smoker	196	55 (28.1)
Current alcohol use	196	91 (46.4)
Country		
France	196	13 (6.6)
Germany	196	35 (17.9)
Ireland	196	3 (1.5)
Netherlands	196	10 (5.1)
Poland	196	42 (21.4)
Qatar	196	3 (1.5)
Romania	196	18 (9.2)
Russia	196	3 (1.5)
Spain	196	11 (5.6)
Switzerland	196	8 (4.1)
UK	196	50 (25.5)
West Europe	196	130 (66.3)
Medical/medication history		
RA duration, months	196	6.38 (2.84)
Prior corticosteroids use	191	73 (38.2)
Prior NSAID use	191	134 (70.2)
Prior DMARDs use	191	25 (13.1)
Number of diseases*	196	2.4 (2.32)
Clinical outcomes		
Patient general health score	196	52.47 (22.71)
Pain assessment score	196	59.04 (21.70)
Patient global assessment score	196	58.4 (23.04)
Physician global assessment score	196	56.43 (16.37)
DAS28	196	5.91 (1.04)
HAQ	194	1.22 (0.64)
Swollen joint count	196	10.29 (5.62)
Tender joint count	196	13.37 (7.02)
FACIT score	193	29.59 (12.07)
PASS (acceptable)	194	48 (24.7)
Quality of life		
EQ-5D index	190	0.49 (0.30)
EQ-5D VAS	191	52.65 (21.48)
SF-36 mental component summary score	192	43.48 (10.75)
SF-36 physical component summary score	192	34.12 (7.69)
Job/workplace		
Employment status		
Full time	196	121 (61.7)
Part time	196	43 (21.9)
Self-employed	196	32 (16.3)
Work habit		
Usually sit	193	69 (35.8)
Stand/walk	193	74 (38.3)
Light loads	193	29 (15.0)
Heavy loads	193	21 (10.9)
Continued		

Table 1 Continued

Variable	N	Mean (SD) or N (%)
Number of work hours per week	196	36.01 (11.90)
Number of work days per week	196	4.87 (0.92)
Multiplier for absenteeism†	101	1.58 (1.64)
Multiplier for presenteeism	196	1.55 (1.72)
Annual income (€)	196	21 588.4 (17 159.9)

*Counting all diseases recorded in medical history categories: cardiovascular history, medical history, RA extra-articular manifestations, and medical history other.
†Only for patients who had any absent hours at baseline.
DAS28, Disease Activity Score based on a 28-joint count; DMARDs, disease-modifying antirheumatic drugs; EQ5D, EuroQol-5 dimensions; FACIT, functional assessment of chronic illness therapy; HAQ, health assessment questionnaire; NSAID, non-steroidal anti-inflammatory drugs; PASS, patient acceptable symptom state; RA, rheumatoid arthritis; SF-36, short form-36; VAS, visual analogue scale.

A total of 115 patients (60.5%) were responders at week 13 and 75 patients were non-responders. We could not categorise six patients into responders or non-responders due to the missing DAS28 data at week 13. Productivity loss for responders and non-responders is clearly shown in figure 2. For responders, each outcome dropped at week 13 and subsequently flattened. For non-responders the outcomes dropped only slightly or even increased (eg, paid work productivity loss) at week 13 and subsequently dropped relatively sharply. This seems to correspond to the progress of disease activity of non-responders. This might be explained by that disease activity of non-responders at week 13 might be improving after week 13, and that those with high disease activity at week 39 withdrew from the study.

In terms of VOLP outcomes during the 1-year study period, overall, paid work productivity loss was 295 h (about 17% of usual working time), unpaid work productivity loss was 162 h, and the total costs were €5223 (table 4). Paid and unpaid work productivity losses for responders (155 and 93 h, respectively) were significantly lower than that for non-responders (522 and 254 h). Total costs of lost productivity for responders (€1993) were significantly smaller than those for non-responders (€10 676).

Table 5 presents marginal effects from models comparing 1 year productivity loss between responders and non-responders (see online supplementary appendix). For 1 year paid work productivity loss, while holding covariates at their mean value at baseline, the expected probability of being zero loss was 44% for responders and 27% for non-responders; the expected paid work hour loss in part 2 of the ZINB model was 266 h and 519 h, respectively; overall, the expected paid work productivity loss was 149 h and 380 h, respectively, with a 231 h significant difference. Similarly, the difference in unpaid work productivity loss was significant and

Table 2 The descriptive statistics of VOLP outcomes by visits

Variable	Baseline	Week 13	Week 26	Week 39	Week 52
Components of paid work productivity loss in the past 3 months					
Follow-up (N)		**193**	**189**	**180**	**157**
Employment status change, N (%)*		23 (11.9)	25 (13.2)	15 (8.3)	11 (7)
Stop working		12 (6.2)	8 (4.2)	4 (2.2)	3 (1.9)
Start working			4 (2.1)	4 (2.2)	2 (1.3)
Change job		1 (0.5)	5 (2.6)	2 (1.1)	2 (1.3)
Change hours		11 (5.7)	12 (6.3)	5 (2.8)	4 (2.5)
Health related status change, N (%)*		20 (10.4)	15 (7.9)	11 (6.1)	3 (1.9)
Stop working		10 (5.2)	5 (2.6)	2 (1.1)	1 (0.6)
Start working			3 (1.6)	4 (2.2)	
Change job		1 (0.5)	1 (0.5)	1 (0.6)	
Change hours		10 (5.2)	7 (3.7)	4 (2.2)	2 (1.3)
Employed	**196**	**181**	**173**	**165**	**143**
Absenteeism (N)	**173**	**154**	**152**	**146**	**130**
Any absent hours, N (%)	101 (58.4)	45 (29.2)	41 (27)	26 (17.8)	15 (11.5)
Percentage of time loss (SD)	0.17 (0.25)	0.09 (0.22)	0.07 (0.22)	0.05 (0.17)	0.03 (0.13)
Absent hours (SD)	75.73 (113.36)	35.15 (91.10)	25.05 (75.27)	16.69 (72.08)	12.04 (48.82)
Presenteeism (N)	**191**	**166**	**160**	**155**	**136**
Any presenteeism, N (%)	75 (39.3)	46 (27.7)	37 (23.1)	37 (23.9)	24 (17.6)
Presenteeism % time loss (N)	**180**	**153**	**147**	**140**	**130**
Percentage of time loss (SD)	0.08 (0.14)	0.05 (0.12)	0.04 (0.12)	0.03 (0.09)	0.03 (0.08)
Paid work productivity loss in the past 3 months (N)	**162**	**153**	**155**	**145**	**135**
Any paid work loss, N (%)	124 (76.5)	73 (47.7)	68 (43.9)	49 (33.8)	40 (29.6)
Percentage of time loss (SD)	0.25 (0.26)	0.2 (0.32)	0.19 (0.34)	0.15 (0.31)	0.13 (0.29)
Paid work loss, hours (SD)	111.71 (116.84)	89.29 (152.60)	83.36 (151.73)	71.7 (156.43)	60.11 (140.91)
Stop working: hour loss (SD)		30.65 (119.48)	36.11 (129.30)	34.92 (132.2)	33.46 (129.61)
Absenteeism: absent hours (SD)	76.75 (115.71)	35.28 (91.39)	24.09 (74.64)	16.01 (72.15)	11.30 (47.90)
Presenteeism: hour loss (SD)	34.97 (58.07)	19.76 (53.65)	16.33 (53.55)	11.94 (36.81)	11.45 (39.55)
Unpaid work productivity loss in the past 7 days (N)	**167**	**176**	**165**	**166**	**143**
Any unpaid work loss, N (%)	86 (51.5)	44 (25.0)	38 (23.0)	34 (20.5)	24 (16.8)
Unpaid work loss, hours (SD)	6.27 (11.11)	3.44 (9.37)	2.73 (7.49)	2.85 (10.68)	1.79 (5.86)
Total costs of lost productivity in the past 3 months (N)	**141**	**143**	**135**	**135**	**124**
Any costs of lost productivity, N (%)	121 (85.8)	79 (55.2)	65 (48.1)	51 (37.8)	44 (35.5)
Total costs, € (SD)	3483.48 (8482.03)	1777.72 (4734.99)	1477.86 (3919.60)	987.46 (2835.20)	842.77 (2242.33)

Bolded numbers are the numbers of patients with non-missing values that were used to generate the statistics below.
*Patients might report changing both job and working hours.
VOLP, The Valuation of Lost Productivity.

Table 3 Change of productivity loss from baseline to week 39/52

Week 39	N*	Week 39—baseline	p Value
Any paid work productivity loss in the past 3 months (%)	125	−44.0	<0.01
Paid work productivity loss in the past 3 months (h)	125	−34.13	0.03
Any unpaid work productivity loss in the past 7 days (%)	145	−29.7	<0.01
Unpaid work productivity loss in the past 7 days (h)	145	−3.88	<0.01
Any costs of lost productivity in the past 3 months (%)	107	−44.9	<0.01
Total costs of lost productivity in the past 3 months (€)	107	−2643.36	0.02
Week 52	**N***	**Week 52—Baseline**	**p Value**
Any paid work productivity loss in the past 3 months (%)	116	−42.2	<0.01
Paid work productivity loss in the past 3 months (h)	116	−33.43	0.03
Any unpaid work productivity loss in the past 7 days (%)	125	−33.6	<0.01
Unpaid work productivity loss in the past 7 days (h)	125	−4.22	<0.01
Any costs of lost productivity in the past 3 months (%)	95	−47.4	<0.01
Total costs of lost productivity in the past 3 months (€)	95	−1322.42	0.02

*The number of patients whose outcomes at baseline and week39/52 were both observed.

equalled 122 h. For total costs of lost productivity, responders had a 32% higher probability of having no costs than non-responders. Overall, responders gained €3670 in productivity compared with non-responders. In the main analysis, we applied the LOCF method to impute the missing data. As a sensitivity analysis, we applied the multiple imputation method and the results were consistent (see online supplementary appendix). After multiple imputations, we found that responders gained €3847 in productivity compared with non-responders. Our results are robust to the two different missing handling methods.

DISCUSSION

The PRIZE study is the first clinical trial to measure the 1-year impact of biological treatment on all the labour input components that affect overall productivity and the corresponding monetary value among people with early RA.[7 10] This study found that paid and unpaid work productivity was significantly improved over 52 weeks. We also compared patients who responded to treatment at week 13 with those who did not to help confirm that it was the achievement of clinical response that produced these changes. For 1 year productivity loss, responders had gained 231 h from paid work and

Figure 1 Study cohort flowchart. DAS28, Disease Activity Score based on a 28-joint count; VOLP, the Valuation Of Lost Productivity questionnaire.
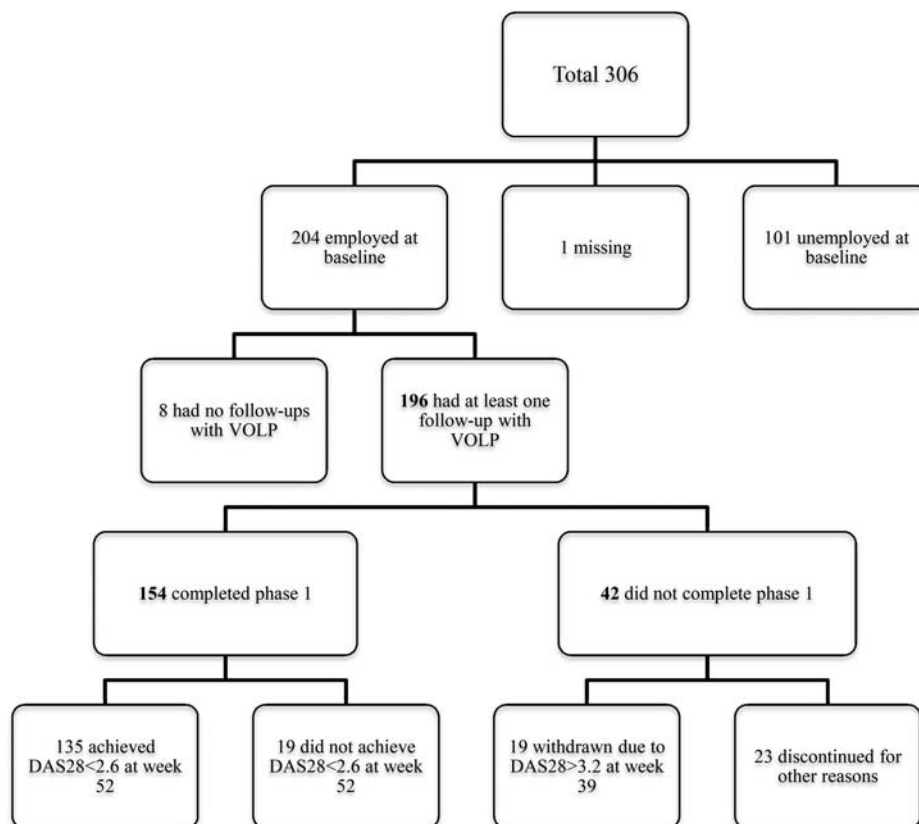
Table 4 Total productivity loss during the 1-year study period by response at week 13

	All	Responder	Non-responder	p Value
Paid work productivity loss (N)	**187**	**111**	**71**	
Paid work productivity loss, hours (SD)	294.97 (506.97)	155.47 (316.35)	521.71 (663.55)	<0.01
Unpaid work productivity loss (N)	**192**	**114**	**73**	
Unpaid work productivity loss, hours (SD)	161.96 (433.01)	93.28 (290.97)	254.48 (570.43)	0.02
Total costs of lost productivity (N)	**184**	**111**	**69**	
Total costs of lost productivity, € (SD)	5522.67 (12 854.38)	1993.48 (4802.50)	10 676.20 (18 594.00)	<0.01

Bolded numbers are the numbers of patients with non-missing values that were used to generate the statistics below.

122 h from unpaid work compared with non-responders, which amounts to an output value of €3670 gained by responders compared with non-responders.

Several previous clinical trials have examined the impact of early aggressive treatment on work productivity in terms of absenteeism among patients with early RA. The PREMIER trial assessed the effect of adalimumab+MTX on absenteeism compared with MTX monotherapy among patients with disease duration <3 years.[25][26] The number of missed workdays due to RA in the first year was 11.1 days and 24 days, respectively.[26] The COMET study measured the effect of ETN+MTX versus MTX on absenteeism among patients with disease duration <2 years and found that the 1-year missed workdays due to health were 14.2 days versus 31.9 days.[6] In the study of Puolakka et al,[5] patients with recent-onset RA (<2 years) were randomly assigned to receive combination therapy of DMARDs or single DMARD. During the 5-year follow-up, they found 23 days of sick leaves per patient-observation year in combination therapy group and 48 days in single therapy group. Our study population was patients with RA ≤1 year and found that the number of missed work hours due to health during 1 year was about 106.9 h, amounting to 14.5 days. Thus, the absenteeism estimates from our study were closer to those from the treatment arm in above studies even

though the design, treatment, RA population and definition of absenteeism differed across studies.

Only one previous clinical trial has estimated presenteeism and unpaid work productivity loss in terms of time loss and costs.[7][10] The PREMIER study measured presenteeism according to a visual analog scale (0–100) but did not translate it into time loss and the associated costs.[25] The COMET study did not directly measure presenteeism among its study participants.[6] The only study that measured and estimated the cost of absenteeism, presenteeism and unpaid work productivity loss was a substudy of CanAct trial.[27] However, this study only evaluated the 12-week impact of adalimumab on work productivity and was not restricted to patients with recent-onset RA.

The main limitation of our study is its single-arm design. By looking at the change in productivity loss over 52 weeks only, we cannot determine whether the change is attributable to the treatment or the natural fluctuations of worker productivity over time especially due to regression towards the mean. Therefore, we compared 1 year productivity loss between responders and non-responders by adjusting for potential confounders. We found that treatment response was associated with a reduction in productivity loss. In this study, if the response was induced by the treatment of ETN plus

Table 5 Expected values by response at week 13 and marginal effects using sample means shown in table 1 from the regression models

	Responder Mean (CI)	Non-responder Mean (CI)	Difference Mean (CI)
Paid work productivity loss			
Probability of paid loss=0 (part 1)	0.440 (0.304 to 0.563)	0.269 (0.124 to 0.376)	0.171 (0.013 to 0.368)*
Mean Loss for part 2 in hours	266 (174 to 344)	519 (312 to 724)	−253 (−469 to −49)***
Mean overall loss in hours	149 (91 to 205)	380 (225 to 558)	−231 (−415 to −77)†
Unpaid work productivity loss			
Probability of unpaid loss=0 (part 1)	0.786 (0.670 to 0.908)	0.427 (0.294 to 0.61)	0.359 (0.149 to 0.545)***
Mean Loss for part 2 in hours	320 (183 to 470)	332 (184 to 369)	−13 (−117 to 217)
Mean overall loss in hours	68 (25 to 120)	190 (89 to 219)	−122 (−166 to −4)†
Total costs of lost productivity			
Probability of total costs=0 (part 1)	0.376 (0.027 to 0.510)	0.058 (0.001 to 0.123)	0.319 (0.023 to 0.466)***
Mean costs for total costs for part 2 in €	4259 (2706 to 6404)	6713 (3285 to 9721)	−2455 (−5362 to 1505)*
Mean overall costs in €	2656 (1583 to 4915)	6326 (3090 to 9246)	−3670 (−6350 to 171)†

***p Value for the coefficients of response variable in the models ≤0.01; **0.01<p≤0.05; *0.05<p ≤0.1.
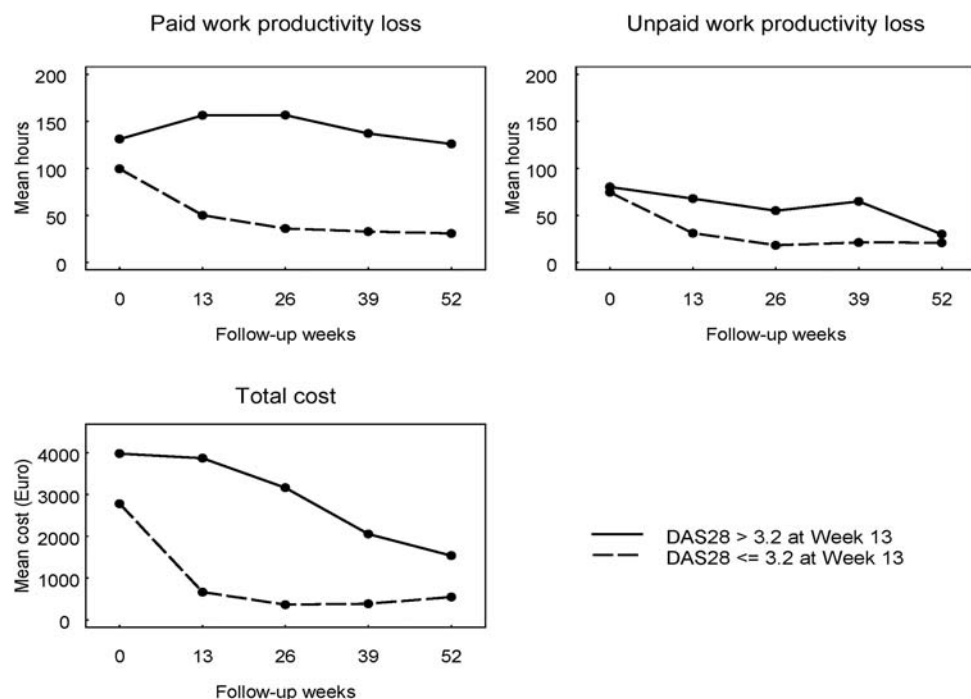†Not applicable.

Figure 2 Plots of 3-month productivity loss and costs at each visit by response at week 13. DAS28, Disease Activity Score based on a 28-joint count.

MTX, then it could be inferred that the cost of ETN therapy can be viewed as being partially offset by cost savings accruing to responders. It is possible that the cost savings would apply to any treatment that induces similar clinical response. However, there might be residual confounding between non-responders and responders although we have put an effort to adjust for potential confounders. For example, in predicting total days of sick leaves and work disability, Olofsson et al[28] found only 21% of the variability was explained by the included predictors. As there might be potential confounders that we did not measure and thus could not adjust for in our study, our estimate of the productivity gain of responders compared with non-responders might be subject to the confounding bias.

In this study, based on the human-capital approach we valued productivity loss by incorporating multipliers that adjust wage to represent the actual impact of the resulting reduced labour input on productivity. As an alternative valuation method, the friction-cost method only takes account of productivity loss within a 'friction period' if absent workdays exceed the period.[29] Productivity loss estimates could be further undervalued if the potential impact of compensation mechanisms is also considered.[30 31] That is, no productivity loss would occur if missed work could be compensated for during normal working hours and the absent worker or colleagues who take over the work do not have to sacrifice their leisure time or take more effort to make up the lost work.[8] In the literature, the choice of valuation method has been debated and there is no current consensus on

appropriate methodology. It should be noted that if applying FC method and considering potential impact of compensation mechanisms in our study, the estimated costs of productivity loss would be smaller.

Our results suggest that patient productivity was significantly improved for those who remained on treatment at week 39 or week 52. Over the 1-year treatment, early responders at week 13 had significant productivity gains compared with non-responders, which suggests this gain was related to treatment response. Future studies should examine treatment effects on paid and unpaid work productivity comprehensively, as this appears to be an important component to improve.

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