Impact of one-year treatment with biotechnological drugs on work ability in patients with rheumatoid arthritis in Italy: a prospective real-life study

M. Manara[1], R. Caporali[2,3], C. Lomater[4], R. Gorla[5], E. Fusaro[6], P. Sarzi-Puttini[7], P. Stobbione[8], S. Capri[9], L. Sinigaglia[1]

[1]ASST Gaetano Pini-CTO, Milan; [2]IRCCS Policlinico San Matteo Foundation, Pavia; [3]Department of Clinical Sciences and Community Health, University of Milan; [4]Ospedale Mauriziano, Torino; [5]Spedali Civili, Brescia; [6]Città della Salute e della Scienza, Torino; [7]L. Sacco Hospital, Milano; [8]Azienda Ospedaliera SS. Antonio e Biagio e Cesare Arrigo, Alessandria; [9]School of Economics and Management, LIUC University, Castellanza, Italy.

Abstract

Objective

We aimed to evaluate the impact of biologic therapy on work productivity outcomes in an Italian real-life cohort of biologic-naïve patients with active rheumatoid arthritis (RA).

Methods

This observational prospective multicentre study enrolled RA patients in working age with an active disease who started their first biologic agent. Every patient completed the RA-specific Work Productivity Survey (WPS-RA) at each clinical evaluation (baseline, 6 and 12 months). The primary outcome of the study was the productivity gain at 12 months from the beginning of the biologic treatment, compared to baseline, assessed in terms of absenteeism and presenteeism reduction, both for employed and unemployed subjects. Linear regression analyses were performed to assess the impact of patient- and disease-related variables on productivity gain.

Results

Overall, 100 patients were enrolled and 85 completed the study. All indexes of disease activity and functional ability were significantly improved from baseline already at 6 months. At 12 months, the 55 employed subjects showed a significant reduction in the mean number of days of work missed (absenteeism) and of reduced productivity (presenteeism). A significant reduction in the mean number of days of household work missed was observed for all patients. At multivariate analysis, functional disability had a significant negative impact on all parameters of household work productivity, while the achievement of a low disease activity or remission was inversely correlated with presenteeism.

Conclusion

One year of treatment with a biological drug significantly impacts on the disease activity and work ability of RA patients and allows economic gains due to productivity improvement.

Key words

rheumatoid arthritis, biological products, work ability

Maria Manara, MD, PhD
Roberto Caporali, MD, Prof.
Claudia Lomater, MD
Roberto Gorla, MD
Enrico Fusaro, MD
Piercarlo Sarzi-Puttini, MD
Paolo Stobbione, MD
Stefano Capri, PhD, Prof.
Luigi Sinigaglia, MD

Please address correspondence to:
Maria Manara,
ASST Gaetano Pini-CTO,
Piazza Cardinal Ferrari 1,
20122 Milano, Italy.
E-mail: maria.manara@gmail.com

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Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory joint disease which can significantly impact on patients' life, leading to activity impairment and disability development. The disease burden may be evaluated not only on a personal level, *i.e.* patient's morbidity, mortality and quality of life, but also in terms of economic and social impact, due to direct costs related to the management of the disease and to indirect costs related to productivity loss (1). Since the prevalence of the disease in Italy is expected to increase in the next years due to a higher life expectancy and an increase in the number of elderly patients, the socioeconomic impact of the disease may become heavier in the next future (2).

RA can affect work productivity at different levels: patients may experience job loss, or days of sick leave from job (absenteeism), but also a reduced productivity while at work (presenteeism) (1). Moreover, the disease can influence work productivity at home and participation in social activities, with consequences not only on economic status but also on self-esteem and quality of life of the patient.

The advent of biological drugs significantly modified the clinical outcome of patients with RA, reducing inflammation and pain and preventing permanent damage. Even if the introduction of these therapies has significantly raised direct medical costs, the treatment with biologics has been widely demonstrated to be associated with an overall improvement of work productivity outcomes, with a variable magnitude of the effect, thus suggesting that the utilisation of these agents may, at least in part, compensate expenditures (3).

As large differences in work productivity outcomes among countries have been observed in patients with RA, due to differences in economic and employment policies as well as in social support of disease-related disability, national data are requested for a more accurate economic evaluation (4). To date, this issue has not been adequately investigated in Italy in large real-life cohorts of patients with RA.

The aim of this study was to evaluate the impact of biologic therapy on work productivity outcomes in an Italian real-life cohort of biologic-naïve patients with active RA.

Methods

Patients

This is an observational prospective multicentre study. Participants were consecutively enrolled among patients referred to 7 Rheumatology tertiary centres in Northern Italy.

Subjects were included if they had a definite RA diagnosis, according to ACR 1987 or ACR/EULAR 2010 classification criteria, and were in working age (18–65 years) (5, 6). Patients included should have an active disease (measured by DAS 28 ≥3.2) and been prescribed their first biologic agent, according to the 2011 guidelines of the Italian Society for Rheumatology [active disease after failure of one or more previous conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs)] (7). Patients in a functional Steinbrocker stage IV were excluded.

At baseline, data about demographics, job activity and education, and employment status were collected. Clinical history including disease duration, previous pharmacological and surgical treatments for RA and comorbidities were retrospectively assessed at the basal evaluation, as well as patient's functional stage according to Steinbrocker classification. According to physician's decision, the presence of erosions was evaluated with hand and forefeet plane radiographs, and the presence and titer of rheumatoid factor and anti-citrullinated protein antibodies were tested.

At baseline and after 6 and 12 months from treatment start, treating physicians performed a clinical evaluation of the patient including indexes of disease activity (ESR-DAS28, SDAI), and the assessment of concomitant medication and adverse events. Patients completed the modified Health Assessment Questionnaire (HAQ) (8).

Every patient completed the RA-specific Work Productivity Survey (WPS-RA) at each clinical evaluation (baseline, 6 and 12 months) (9). The questionnaire assessed the number of days of work missed (absenteeism) and the number of days in which work produc-

tivity was reduced ≥50% (presenteeism) in the previous months, concerning both work outside home and at home, as well as the number of days in which social activities were impaired by the disease. The rate of arthritis interference with work productivity outside and within home in the previous month was measured on a numeric rating scale (from 0: no interference, to 10: complete interference). Only employed subjects completed questions pertaining paid job (Q2-Q4), while all patients answered questions addressing unpaid work within home and social activities (Q5-Q9). An Italian version of the WPS-RA was obtained by forward and backward translation of the original English version and subsequently validated on a sample of 10 patients.

The study was approved by the local Ethics Committees. All the participants subscribed an informed consent before the inclusion in the study and the study was conducted in accordance with the ethical principles of the Declaration of Helsinki.

Outcome assessment

The primary outcome of the study was the productivity gain at 12 months from the beginning of the biologic treatment, compared to baseline. The productivity gain was assessed for employed subjects as the reduction in the number of days of work missed (absenteeism) or in the number of days in which work productivity was reduced ≥50% (presenteeism). For unemployed patients, we evaluated the number of days of household work missed and the number of days in which household work productivity was reduced ≥50%.

Secondary outcome was the assessment of the productivity gain at 6 months from the start of the biologic treatment.

The economic impact of productivity loss for employed subjects was estimated considering both absenteeism and presenteeism. Based on the average gross national wage, according to 2017 estimates, we calculated the average hourly earnings. For absenteeism, the mean number of days of work loss in the previous month was multiplied by the average daily earnings, assuming 8 working hours a day. For presenteeism, since patients reported that "work productivity was reduced almost of 50%", we assumed 4 working hours a day.

Statistical analysis

Baseline characteristics of the study population were described in terms of mean (standard deviation, SD) or median (interquartile range, IQR) for continuous variables, according to their distribution, and number (percentages) for categorical variables. Comparisons with baseline data were performed with *t*-test for paired data for normally distributed variables or Wilcoxon test for variables without normal distribution.

Multivariate linear regression analysis was performed to assess the impact of patient-related variables (age, sex) and disease-related variables (disease duration, functional disability and target achievement, *i.e.* low disease activity or remission, at 12 months) on productivity gain, evaluated with the WPS-RA questionnaire.

The sample size was calculated for paired data, considering a mean of the paired differences in overall working impairment of 15.2 and a standard deviation of the paired differences of 24.6 (10). According to these data, the study would require a sample size of 24 employed subjects to achieve a power of 80% and a level of significance of 5% (two sided) in detecting a difference between pre- and post-treatment values. Assuming a percentage of 40% employed subjects in our population, the total number of patients included would be 60. To allow for 40% of patients to discontinue therapy, the estimated sample size was 100 subjects. Sample size for paired differences was calculated with the online calculator Statulator (11).

Results

From January 2014 to February 2016 102 patients were screened. After exclusion of 2 patients who did not satisfy inclusion criteria, 100 patients were enrolled in the study. Among them, 85 were female; subjects had a mean age of 48,9 (SD: 10.2) years and a mean disease duration of 7 (IQR; 3–14) years. Among 56 patients who performed an x-ray of hands or forefeet, 27 (48%) showed erosions. Rheumatoid factor positivity was found in 71% cases, and ACPA positivity in 69%. At baseline all patients had an active disease, with a mean DAS28 of 5.1 (SD: 0.9) and a median SDAI of 25.2 (IQR: 18.7–33.2). Steinbrocker class I was calculated in 19 patients, II in 67 patients and III in 14 patients; median HAQ-DI was 1 (IQR: 0.75–1.8).

At baseline, 55 subjects were employed. Among those unemployed, 25 were housewives, 8 retired, 2 students, 4 unable to work, 6 were volunteers or not otherwise specified. The first biologic drug prescribed was a TNF-inhibitor in 68 patients, abatacept in 24 subjects and tocilizumab in 8 patients. Patients' characteristics at baseline are reported in Table I.

At 12 months, 85 subjects were still on follow-up; 14 patients had switched to another biological drug. Among pa-

Table I. Characteristics of the study population at baseline.

	Baseline
Age, mean (SD)	48,9 (10,2)
Sex (female), n (%)	85 (85%)
Disease duration (years), median (IQR)	7 (3-14)
Rheumatoid Factor positive, n (%)	71 (71%)
ACPA positive, n (%)	69 (69%)
Erosive, n (%)	27 (48%) of 56
Steinbrocker functional status, n (%)	
-I	19 (19%)
-II	67 (67%)
-III	14 (14%)
Education, n (%)	
-elementary school	8 (8%)
-middle school	46 (46%)
-high school	31 (31%)
-university degree	11 (11%)
-not reported	4 (4%)
Occupation, n (%)	
-employed	55 (55%)
-housekeeper	25 (25%)
-retired	8 (8%)
-student	2 (2%)
-unable to work	4 (4%)
-other	6 (6%)
Biological treatment, n (%)	
-Abatacept	24 (24%)
-Adalimumab	21 (21%)
-Certolizumab pegol	5 (5%)
-Etanercept	35 (35%)
-Golimumab	6 (6%)
-Infliximab	1 (1%)
-Tocilizumab	8 (8%)

SD: standard deviation; n: number; IQR: interquartile range.

tients who dropped out, 6 experienced adverse events, 2 patients stopped the treatment for inefficacy, and 7 subjects retired the consent or were lost at follow up (Fig. 1).

Patients who persisted on treatment experienced a significant improvement from baseline in all indexes of disease activity and functional ability at 12 months (Table II). A significant improvement was already observed at 6 months, with a further improvement in HAQ and Global Health Assessment from 6 to 12 months.

According to the results of the WPS-RA questionnaire at 12 months, patients employed had a significant reduction in the mean number of days of work missed (absenteeism) and in the number of days of reduced productivity (presenteeism) (Table III). A significant reduction in the rate of arthritis interference with work productivity was also observed for these subjects.

Patients who completed the WPS-RA questionnaire at 12 months, reported a significant reduction in the mean number of days of household work missed and in the number of days in which the productivity in household work was reduced. Moreover, we observed a significant reduction in the number of days in which the disease inhibited social activities and in the number of days in which the patient needed outside help to perform everyday activities at home. The rate of arthritis interference with household work productivity was significant reduced at 12 months compared to baseline (Table III). A significant improvement in all these parameters was already observed at 6 months and remained stable until 12 months.

A multivariate linear regression analysis was performed to evaluate the impact of age, sex, disease duration, functional disability at 12 months (HAQ ≥1) and therapeutic target achievement at 12 months (low disease activity or disease remission, *i.e.* a DAS 28 <3.2) (7) on the different parameters of work ability assessed by WPS-RA questionnaire. While functional disability had a significant negative impact on all parameters of household work productivity (Q5–Q9), the achievement of a low disease activity or remission was inversely correlated with the number of days of reduced productivity at work (presenteeism, Q3) and with the rate of arthritis interference with work productivity outside and within the home (Q4, Q9).

Considering an average gross national wage of €28,250 (12), we estimated the average hourly earnings to be €16.05 (assuming 220 working days per year and 8 working hours per day). Therefore, we calculated a mean monthly loss due to absenteeism of € 334 per person at baseline, and a mean monthly loss of €77 per person at 1 year from treatment start, with a mean monthly difference of €257 (economic gain due to absenteeism reduction related to the treatment). While considering presenteeism, we estimated a mean monthly loss of €353 per person at baseline, and a mean monthly loss of €45 per person at 1 year from treatment start, with a mean monthly difference of € 308 (economic gain due to presenteeism reduction related to the treatment).

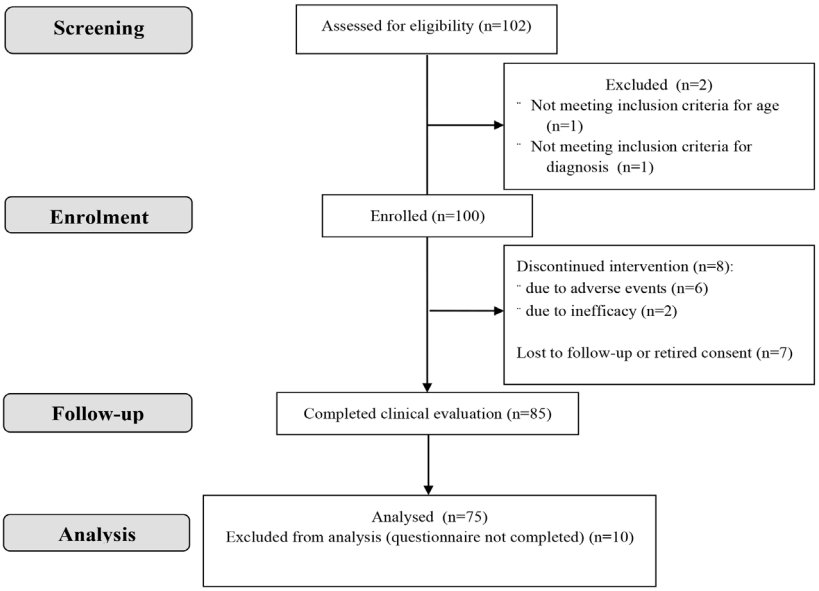

Fig. 1. Flow diagram of patients enrolled in the study.

Table II. Clinimetric indexes at baseline, 6 months and 12 months.

	Baseline (n=100)	6 months (n=90)	12 months (n=85)
VAS patient (0-10) [median (IQR)]	7 (5; 8)	3 (1; 5)*	2 (0; 5)*
VAS physician (0-10) [median (IQR)]	5 (4; 7)	2 (0; 3)*	1 (0; 3)*
Patient's global health assessment (0-100) [median (IQR)]	55 (40; 70)	30 (5; 60)*	19 (3; 50)*§
HAQ score [median (IQR)]	1 (0.75; 1.8)	0.6 (0; 1)*	0.25 (0; 0.87)*§
DAS 28 [mean (SD)]	5.1 (0.9)	3.1 (1.4)*	2.8 (1.3)*
SDAI [median (IQR)]	25.2 (18.7; 33.2)	7.7 (2.4; 14)*	5.1 (1.9; 12.9)*

*p<0.05 compared to baseline; t-test for paired data for normally distributed variables, Wilcoxon test for variables without normal distribution; §p<0.05 compared to 6 months; t-test for paired data for normally distributed variables, Wilcoxon test for variables without normal distribution.
n: number; IQR: interquartile range; SD: standard deviation.

Discussion

In this prospective real-life multicentre study on Italian patients with RA, the prescription of a first biologic drug, according to national guidelines, was associated with a significant improvement of work productivity outcomes after 1 year, both outside and within home.

At multivariate analysis we observed that the achievement of the therapeutic target according to the previous and more recent Italian Society for Rheumatology guidelines, *i.e.* a low disease activity or remission based on DAS28 (7, 13), was associated with a reduced subjective impact of arthritis on work both outside and within home, and with a significant lower rate of presenteeism. This finding is in

Table III. Number of days of activity impairment and rate of arthritis interference with work productivity according to WPS-RA questionnaire, at baseline, 6 months and 12 months.

	Baseline [mean (SD)]	6 months [mean (SD)]	12 months [mean (SD)]
Employed	(n=55)	(n=45)	(n=37)
Q2: Number of days of work missed (absenteeism)	2.6 (4.8)	0.8 (3.2)*	0.6 (1.5)*
Q3: Number of days of reduced productivity (presenteeism)	5.5 (7.7)	0.9 (2.3)*	0.7 (1.5)*
Q4: Rate of arthritis interference with work productivity (0-10 points scale)	4.3 (2.8)	1.4 (2.4)*	1.1 (1.9)*
All patients	(n=99)	(n=82)	(n=75)
Q5: Number of days of household work missed	6.7 (8.5)	3.4 (7.3)*	2.7 (5.2)*
Q6: Number of days of reduced productivity in household work	9.1 (9.9)	2.8 (5.1)*	2.7 (5.2)*
Q7: Number of days with social activities missed	6.2 (8.9)	2.1 (5.3)*	1.9 (4.8)*
Q8: Number of days with outside help	5.7 (8.4)	1.9 (5.1)*	1.5 (4.6)*
Q9: Rate of arthritis interference with household work productivity (0-10 points scale)	6.1 (2.7)	2.8 (2.9)*	2.9 (2.9)*

*$p<0.05$ compared to baseline; *t*-test for paired data. SD: standard deviation; n: number.

line with the observation that in patients with spondyloarthritis the index of disease activity ASDAS-CRP had a higher correlation with presenteeism than with absenteeism (14). However, according to the multinational COMORA study, the impact of RA on absenteeism in Italy seems to be lower than in other countries with a lower gross domestic product, but the risk of presenteeism higher, thus suggesting that in Italian population presenteeism may represent the most reliable indicator of work disability for patients with RA (15).

On the other hand, we observed that patient's disability, evaluated with the HAQ, impacted mainly on parameters assessing work productivity at home. A possible explanation of this finding relies on similarities between questions assessing the impact of RA on household work productivity in the WPS-RA questionnaire and questions assessing disability related to RA in the HAQ. Moreover, we can hypothesise that patients who had developed a disease related disability before starting biologic treatment could have been forced to stay at home, as loss of work capacity mainly occurs during the first years of disease (16).

We did not observe any effect of disease duration on work ability outcomes, but it must be underlined that patients included in our cohort had a long median disease duration (7 years). In a study on RA patients included in the Swedish biologic register (ARTIS), starting a treatment with anti-TNF drugs within 5 years from the disease onset was associated with a higher probability of regaining work ability compared to later starts (17). However, the same authors observed that disability status at the time of biologic therapy initiation affected work ability more than disease duration, suggesting that treatment with biologic drugs should be started early, before permanent work disability occurs.

In this study we tried to quantify the economic gain related to work ability improvement due to biologic therapy in employed subjects enrolled in our cohort of patients with RA. Monetising indirect costs due to work ability impairment is very challenging since there is no consensus about the best measure to be used, especially for presenteeism (1). We used the "human capital approach" method, which allows calculating the loss of income from work disability by a societal perspective (18). Loss of income due to absenteeism was calculated multiplying the number of days in which patients were absent from work by the average national income, while the costs due to presenteeism were calculated based on the assumption that patient's productivity at work was reduced of a half, *i.e.* considering 4 working hours per day instead of 8. Other methods for measuring costs related to presenteeism use multipliers that can extremely vary among different instruments and lead to very different cost estimates (19). The estimates emerging from our cohort are in line with results from other studies (3). In our cohort, monthly gain due to absenteeism reduction was calculated as €257 (*i.e.* about €3000 per year) and monthly gain due to presenteeism reduction was calculated as € 308 (*i.e.* about €3700 per year). Although these results may be regarded as explorative because they do not represent the principal outcome of the study, and despite methodological issues previously discussed, this data represents the first estimate of the economic gain related to work ability improvement due to biologic therapy in patients with RA in Italy (2). The importance of results specific for national populations comes from the observation that the impact of RA on work ability may extremely vary in different countries (15) and that values of productivity estimates are dependent on the local healthcare system (3). Moreover, these results further support the major role of presenteeism in assessing the impact of RA on work ability, since from our estimates the economic gain due to treatment with biological drugs seems to be higher when considering presenteeism than absenteeism in our cohort. As reported in other studies, presenteeism may be the principal determinant of costs related to reduced productivity in RA (20).

Indeed, it must be underlined that a complete assessment of gains related to the treatment is hard to perform, since indirect costs related to the disease are difficult to estimate and may overcome direct costs (21). Moreover, the impact of work ability on patient's quality of life is wide and concerns also other "intangible" values, like self-esteem and sense of purpose, that cannot be properly addressed by an economic evaluation (1).

The main strength of our study is that this is the first real life prospective study on Italian population *ad hoc* designed to evaluate the impact of biologic treatment on work ability in RA. Patients included in the cohort were treated according to national guidelines, both in academic and in hospital settings. The direct clinical evaluation of the patient by a rheumatologist assures the reliability of diagnosis and clinical parameters assessment. Moreover, the study focused on a class of drugs (biologic agents) and not on a single drug, as most of the existing studies on this topic.

The use of the WPS-RA questionnaire allows a wide evaluation of the impact of the disease on work ability, including not only parameters related to employed job (absenteeism, presenteeism), but also those related to domestic work and social activities. According to a recent OMERACT survey, the WPS-RA questionnaire is considered one of the best performing instruments to assess work ability in subjects with RA (22-24).

The main limit of this study is the absence of a control group of patients with RA treated only with csDMARDs. However, as the treatment with biological drugs was prescribed according to national guidelines, *i.e.* in subjects with an active disease after failure of one or more previous csDMARDs, continuing a treatment with a csDMARD instead of starting a biologic would be considered unethical in this setting. The small number of employed subjects in the cohort may have limited the power of multivariate analysis. Moreover, all patients were followed in rheumatology centres of Northern Italy, and this may affect the representativeness of Italian population. Lastly, we did not assess the impact of comorbidities and other disease-related variables such as fatigue, that could have a significant influence on work ability (25, 26).

Conclusions

The results of this real-life study on an Italian cohort of patients with RA suggest that the first year of treatment with a biological drug significantly impacts on disease activity and work ability. A treat-to-target strategy aimed at achieving a low disease activity or remission may improve patient's productivity at work, while the effect of the treatment in reducing disability may allow better performances also in household work and social activities. Estimates of economic gains due to productivity improvement suggest that the use of biological agents may, at least in part, compensate direct medical costs related to the treatment.

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