ORIGINAL ARTICLE

Work Productivity Loss in Early Arthritis During the First 3 Years of Disease: A Study From a French National Multicenter Cohort

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Objective. To assess work productivity (WP) loss during the first 3 years of disease in a cohort of patients with early arthritis (EA) diagnosed between 2002 and 2005.

Methods. The ESPOIR (Etude et Suivi des Polyarthrites Indifférenciées Récentes) cohort included 813 EA patients; we included those of working age at baseline in the present study. WP loss was assessed by 3 components: sick leave, permanent disability, and early retirement. The proportion of affected patients and the mean number of days off work were assessed for each component. WP costs were estimated and determinants of positive and extreme costs were assessed by logistic regression models.

Results. Among the 664 patients included, 81.6% were in the workforce at baseline. During the first 3 years of disease, 45% reported at least 1 sick leave day and 11% reported permanent disability. Only a few patients (1%) reported early retirement. The mean number of days on sick leave due to EA decreased regularly from 44 to 13, whereas the mean number of days on permanent disability tripled from 10 to 33. The mean annual cost was €1,333 (95% confidence interval €1,075–1,620). Sick leave longer than 30 days due to EA before inclusion and a decrease in mental and physical scores of the Medical Outcomes Study Short Form 36 at inclusion were independent determinants of positive and extreme costs in multivariate models.

Conclusion. WP loss is substantial in EA patients and is due to permanent disability before the third year of disease. Work absence and poor mental and physical health status at baseline are major determinants of WP costs.

INTRODUCTION

Rheumatoid arthritis (RA) is a disabling disease that typically affects people of working age, often resulting in absence from the work place (i.e., absenteeism), then job cessation (1–3). This situation has major consequences for society in terms of high economic burden and for individual patients. Some studies have reported that job cessation can itself lead to depression and decreased self-esteem, and have highlighted the importance of work for people's well-being (4–6). Recently, thanks to a better RA prognosis with a tight control strategy and therapy with new biologic agents, work productivity (WP) has become a strategic

outcome with the idea that better control of RA should lead to reduced absenteeism (7,8). Therefore, WP assessment is now central to determining the overall health benefit to patients, as well as the potential economic benefit that society may expect from new treatments, which are of substantially higher cost (9,10).

Before the era of therapy with a biologic agent, RA resulted in significant absenteeism and therefore substantial productivity losses (11,12). The first years of disease were found to be particularly important in establishing permanent disability and high disability costs (13–15). Recently, some studies have analyzed the impact of ther-

Significance & Innovations

- Work productivity loss is substantial, even at arthritis onset.
- Although sick leave is predominant during the first 2 years of disease, permanent disability is already the major component of work productivity loss during the third year.
- Patients who have already stopped working will stop working: an absence from work longer than 30 days before inclusion is a major determinant of work productivity costs.

apy with new biologic agents and treatment strategies on WP in RA patients, reporting a decrease in WP loss, but most of these studies were controlled trials over short periods and often enrolled patients with established RA (16–23). Indeed, we lack longitudinal studies evaluating the effect of biologic agents on WP and its costs in early arthritis.

Assessment of predictors of WP loss is a key issue in recognizing at-risk patients at the start of the disease to prevent job loss. Predictors most frequently identified include demographic markers (e.g., older age, less education), disease markers (e.g., long disease duration, high functional disability, high disease activity), and job markers (e.g., manual or physically demanding jobs) (24,25). The importance of contextual factors in job retention (e.g., family support, telling coworkers about RA) is also recognized, but often difficult to capture (26–28).

We aimed to assess paid WP loss and its associated public costs and identify factors associated with positive and extreme costs in a multicenter cohort of early arthritis patients receiving standard treatment during the first 3 years of disease.

PATIENTS AND METHODS

Patient selection. The ESPOIR (Etude et Suivi des Polyarthrites Indifférenciées Récentes) cohort is a French national multicenter cohort of early arthritis patients enrolled from 2002–2005, in hospitals or in private practice. Patients were followed every 6 months in the first 2 years and are now being followed every year, with an expected followup of 10 years. Inclusion criteria were ≥2 swollen joints and a history of swollen joints lasting between 6 weeks and 6 months (29). Among the 813 patients included in the ESPOIR cohort, 76.7% were women, 44.2% were rheumatoid factor (RF) positive, and 71.3% fulfilled the 1987 American College of Rheumatology (ACR) criteria for RA after 2 years of disease (30). For the present evaluation, we included only patients of working age (<60 years). The protocol of the ESPOIR cohort study was approved by the ethics committee of Montpellier, France. All patients gave their signed informed consent before inclusion.

Patient characteristics. We used a self-reported questionnaire to collect baseline data on demographic characteristics (age, sex, ever smoker, education status, occupational category), time to see a rheumatologist (delay between the first symptom and the first visit to a rheumatologist), disease characteristics (Disease Activity Score in 28 joints [DAS28], Health Assessment Questionnaire [HAQ] score, elevated level of C-reactive protein [CRP; yes/no], positivity for RF and anti–cyclic citrullinated peptide [anti-CCP] antibody status [yes/no], fulfillment of the 2010 ACR/European League Against Rheumatism [EULAR] classification criteria for RA, and radiographic evidence of erosions [yes/no]), as well as mental component summary (MCS) and physical component summary (PCS) scores from the Medical Outcomes Study Short Form 36 (SF-36), a quality of life instrument (31,32).

Job status (full time or part time, permanent disability, retirement, unemployment, housewife/-husband, and student) and job characteristics (job title, number of hours worked per week, and percentage of full-time work load for part-time job) were collected at baseline and at each followup visit.

WP loss. WP loss was divided into 3 components: sick leave, permanent disability, and early retirement. At each followup visit, patients used a self-reported questionnaire to report cumulative number of days off work for sick leave, date of disability status and disability category for permanent disability, and early retirement, each time related to early arthritis (see Supplementary Appendix A, available in the online version of this article at http://onlinelibrary.wiley.com/doi/10.1002/acr.22298/abstract). The recall period was 6 months during the first 2 years, and then 1 year thereafter. Because the date of early retirement was not specified in the questionnaire, if a patient reported being in early retirement at a followup visit, the number of retired days corresponded to the entire period preceding the followup visit.

WP cost estimation. Costs were estimated from the public payer perspective, i.e., only compensation costs received by each patient for not being at work. Sick leaves and permanent disability compensations were determined according to publicly available data from the French National Health Insurance and early retirement compensations were determined according to the French National Retirement Insurance. Because sick leave compensation depends on income, an average income was attributed to each patient according to the patient's sex and occupational category with 2005 data from the national labor statistics institute (INSEE, online at http://www.insee.fr/fr/ffc/tef/tef2013/T13F051%5CASF_041DD16.xls). In France, permanent disability compensations also depend on civil servant status (only civil servant patients receive 100% of their income the first 3 years before receiving a disability pension, depending on the disability category). Because this pattern (civil servant or not) was not directly collected in the ESPOIR questionnaire, 2 authors (SD and BF) independently classified patients as a civil servant or not using the

job denomination reported by the patient. Differences in classification were resolved by consensus after discussion.

Statistical analyses. Descriptive statistics are expressed as the mean ± SD for quantitative variables and as the number (percentage) for categorical variables. Data collected every 6 months during the first 2 years of followup were summed to express data per year.

For each WP loss component, we estimated the mean number of days off work and the percentage of affected patients by year. Mean costs were calculated by component and by year. We estimated 95% confidence intervals (95% CIs) by bootstrapping (1,000 replications) (33). All costs were expressed in 2005 Euros. WP loss components and costs were compared to those of the general population in France based on the 2005 French National Health Insurance data (34,35).

Determinants of WP costs. WP costs were assessed by 2 logistic models. In the first model, the binary outcome was the presence or not of costs over the study period. For the second model, the binary outcome was the presence of extreme costs, defined by the cost distribution curve as >€10,000 over the study period for patients with positive costs. Both logistic regressions involved data for patients attending all 4 followup visits (n = 467 and n = 243, respectively). Potential determinants of WP costs (independent variables) were derived from different domains. Demographic characteristics included sex, age at diagnosis, postsecondary education (yes/no), smoking history (yes/no), and manual work (craftwork/shop keeper, non-professional, or farmer [yes/no]). Disease characteristics included DAS28, HAQ score, anti-CCP positivity, CRP positivity, RF positivity, 2010 ACR/EULAR criteria fulfilled for RA, and radiographic evidence of erosions. Psychological and behavioral factors, including the MCS and PCS scores of the SF-36, and previous sick leave longer than 30 days due to early arthritis before inclusion were also added. Logistic regression was used to model the association between independent variables and each of the binary outcomes of interest. For each model, a *P* value of 0.20 on bivariate analysis was required for inclusion in the multivariate analysis. Variables were chosen by a backward selection method. Hosmer-Lemeshow goodness of fit was used to assess the model fit.

Management of missing data and sensitivity analyses. For the main analysis, costs were calculated for each year with no imputation of missing data. Because missing data were mostly due to patients not attending followup, data were assumed to be missing at random (MAR). To assess the sensitivity of the analysis to the MAR assumption, we developed 5 scenarios. In the first scenario, only patients fulfilling the 2010 ACR/EULAR classification criteria for RA at baseline were included. In the second scenario, only patients who attended all 4 followup visits were included. Simple imputation was used for the third and fourth scenarios to model missing values at each time: by imputing a mean cost per period based on all attending patients adjusted by sex and occupational category and by imputing the last costs for the affected patient (last observation carried forward method). In the fifth scenario, we performed multiple imputations using the Multivariate Imputation by Chained Equations (MICE) procedure (package MICE of R) (36).

For the main analysis, we performed both logistic regression analyses for patients attending all 4 followup visits. In the sensitivity analysis, MAR data were imputed by use of the MICE procedure 5 times. Each time, we used both multivariate models and Akaike's information criterion backward selection to identify determinants of positive and extreme costs.

All statistical analyses involved use of SAS, version 9.3 and R (http://www.r-project.org, R Foundation for Statistical Computing).

RESULTS

Characteristics of patients. Among the 813 patients included in the ESPOIR cohort between 2002 and 2005, 664 were of working age (<60 years). The mean ± SD age was 44.2 ± 10.8 years, the mean ± SD disease duration (mean delay between the first swollen joint and inclusion) was 75.4 ± 79.7 days, and 78.5% were women (Table 1). After 3 years of followup, the mean ± SD DAS28 was 2.87 ± 1.39, 77.6% of patients received a disease-modifying antirheumatic drug, and 15.7% received treatment with a biologic agent.

Patients with WP loss. A total of 299 patients (45%) reported at least 1 day off work due to early arthritis during the first 3 years of followup. Before enrollment in the study, 107 patients (16.1%) reported more than 30 days of sick leave due to early arthritis in the last 6 months.

The proportion of patients affected by WP loss (sick leave, permanent disability, or early retirement) decreased between the first and second year, from 37.1% to 32.3%, and then stabilized thereafter. The proportion of patients on sick leave decreased over the 3 years, from 32.1% to 17.5%, but patients on permanent disability reached 11.2% at the third year. The proportion of patients on sick leave and on permanent disability was much higher than in the general population, with 6.8% in sick leave and 1.1% in permanent disability (Figure 1). Only a few patients (1.0%) were in early retirement because of early arthritis over the followup period.

Number of days off work. The mean number of days off work due to early arthritis among the study population decreased slightly over the 3 years, from 63.3 to 50.6 days. The decreasing number of days on sick leave per year, from 44 to 13 days, was counterbalanced by an increasing number of days off work due to permanent disability per year, from 10 to 33 days, over the study duration. In 2005, a mean of 4.8 days on sick leave per person per year was reported for the general population.

WP costs. For patients attending all followup visits over the 3 years, the mean annual cost was €1,333 (95% CI €1,075–1,620; median €0, interquartile range €0–342). For sick leave and permanent disability components, the cost

Table 1. Demographic and disease characteristics of the 664 patients of working age with early arthritis at baseline*			
	All (n = 664)	Men (n = 143)	Women (n = 521)
Demographic characteristics			
Sex		21.5	78.5
Age, mean ± SD years	44.2 ± 10.8	45.7 ± 10.2	43.7 ± 10.9
Workforce population	81.6	90.6	79.2
Full-time job	62.9	83.9	57.2
Part-time job	13.3	3.5	15.9
Unemployed	5.4	3.2	6.1
Nonactive population	18.4	9.4	20.8
Occupational category			
Farmer	2.6	3.1	2.5
Craftwork, shop keeper	5.2	10.1	3.9
Administrative, sales, or service occupations	53.0	32.1	58.7
Nonprofessional	10.3	25.8	6.1
Intermediary occupations	15.4	14.8	15.5
Manager, accredited professional	13.5	14.1	13.3
Disease characteristics			
Disease duration, mean ± SD days	75.4 ± 79.7	75.7 ± 60.4	75.3 ± 84.3
DAS28, mean ± SD	5.06 ± 1.28	5.02 ± 1.34	5.06 ± 1.28
CRP positive	44.5	60.1	40.2
HAQ score, mean ± SD	0.96 ± 0.67	0.94 ± 0.64	0.97 ± 0.68
Anti-CCP positive	40.7	47.5	38.8
Rheumatoid factor positive	47.1	50.3	46.1
2010 ACR/EULAR classification criteria fulfilled	79.0	77.5	79.4
Radiographic evidence of erosion	13.3	19.0	11.7
MOS SF-36			
MCS score, mean ± SD	39.6 ± 10.9	40.8 ± 11.0	39.2 ± 10.8
PCS score, mean ± SD	37.4 ± 8.9	36.1 ± 7.9	37.7 ± 9.1

* Values are the percentage unless indicated otherwise. DAS28 = Disease Activity Score in 28 joints; CRP = C-reactive protein; HAQ = Health Assessment Questionnaire; anti–CCP = anti−cyclic citrullinated peptide antibody; ACR = American College of Rheumatology; EULAR = European League Against Rheumatism; MOS SF-36 = Medical Outcomes Study Short Form 36; MCS = mental component summary; PCS = physical component summary.

varied widely over the 3 years (Figure 2). In 2005, costs due to sick leave and permanent disability in the general population were €130 and €120 per person, respectively, corresponding to 10% of the early arthritis costs.

Determinants of positive and extreme WP costs. Among the 467 patients who attended all followup visits, 243 (52.0%) had WP costs. Anti-CCP positivity (odds ratio [OR] 2.16 [95% CI 1.44−3.25], $P < 0.001$), a 1-point de-
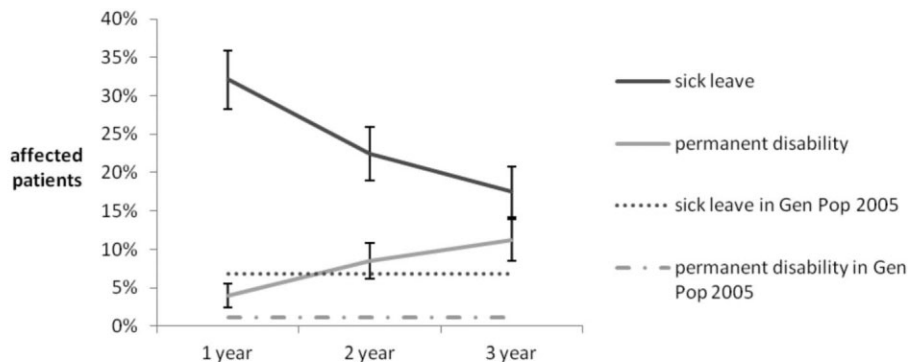
Attending patients	n = 579	n = 544	n = 509
Patients with WP loss, n (%)	215 (37.1%)	176 (32.3%)	151 (29.7%)

Figure 1. Percentage of patients with work productivity (WP) loss during the first 3 years of early arthritis, considering sick leave and permanent disability and compared to the general population (Gen Pop).
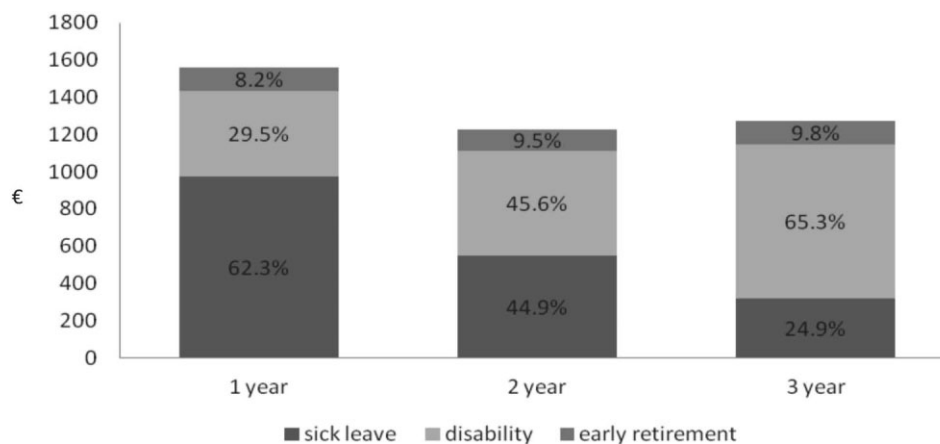
Figure 2. Mean work productivity (WP) cost (with median and interquartile range [IQR]) during the first 3 years of early arthritis, by WP component. Ninety-five percent confidence intervals (95% CIs) were assessed by bootstrapping.

crease in MCS score (OR 1.04 [95% CI 1.02–1.06], $P < 0.001$) corresponding to deteriorated mental health, and sick leave due to early arthritis longer than 30 days before inclusion (OR 9.89 [95% CI 4.53–21.55], $P < 0.001$) were

independently associated with having costs on multivariate analysis (Table 2).

Among the 243 patients attending all followup visits and with WP costs, 64 (26%) had costs >€10,000, defined

Table 2. Univariate and multivariate logistic regression analysis of potential predictors of incurring costs associated with early arthritis and work productivity loss*

	Costs = €0 (n = 224)	Costs >€0 (n = 243)	Univariate P	Multivariate analysis	
				OR (95% CI)	P
Demographic factors					
Male sex	17.0	25.1	0.03		0.31
Age, mean ± SD years	45.8 ± 10.3	44.6 ± 10.3	0.21		
Educational level (after graduation)	37.0	31.3	0.19		0.52
Smoking status (ever smoker)	47.8	50.6	0.54		
Manual job	19.0	21.1	0.59		
Time to see the rheumatologist, mean ± SD days	77.0 ± 91.0	76.8 ± 79.7	0.98		
Disease characteristics					
DAS28, mean ± SD	4.88 ± 1.31	5.30 ± 1.25	< 0.001		0.31
HAQ score, mean ± SD	0.85 ± 0.65	1.08 ± 0.70	< 0.001		0.08
Anti-CCP positive	38.4	53.5	0.001	2.16 (1.44–3.25)	< 0.001
CRP positive	39.3	47.7	0.07		0.38
Rheumatoid factor positive	46.0	54.3	0.07		0.88
2010 ACR/EULAR classification criteria fulfilled	82.1	84.3	0.52		
Radiographic evidence of erosion	15.2	13.6	0.62		
Psychological and behavioral factors					
MCS score, mean ± SD	42.4 ± 10.8	37.8 ± 10.5	< 0.001	1.04 (1.02–1.06)†	< 0.001
PCS score, mean ± SD	39.0 ± 8.9	35.5 ± 8.5	< 0.001		0.05
Other					
Sick leave >30 days before inclusion	3.6	27.8	< 0.001	9.89 (4.53–21.55)	< 0.001

* Values are the percentage unless indicated otherwise. Hosmer-Lemeshow goodness-of-fit test: $\chi^2 = 5.03$, 8 df, $P = 0.75$, concordance index = 0.736. OR = odds ratio; 95% CI = 95% confidence interval; DAS28 = Disease Activity Score in 28 joints; HAQ = Health Assessment Questionnaire; anti-CCP = anti–cyclic citrullinated peptide antibody; CRP = C-reactive protein; ACR = American College of Rheumatology; EULAR = European League Against Rheumatism; MCS = mental component summary; PCS = physical component summary.
† OR for the MCS score is for a 1-point decrease.

Table 3. Univariate and multivariate logistic regression analysis of potential predictors of extreme costs*

	€0 <costs <€10,000 (n = 179)	Costs ≥€10,000 (n = 64)	Univariate P	Multivariate analysis OR (95% CI)	P
Demographic factors					
Male sex	24.0	28.1	0.52		
Age, mean ± SD years	42.94 ± 10.4	49.2 ± 8.5	< 0.001	1.56 (1.13–2.15)†	0.001
Educational level (after graduation)	36.9	15.6	0.002		0.29
Smoking status (ever smoker)	48.6	56.2	0.29		
Manual job	18.5	28.1	0.11		0.91
Time to see the rheumatologist, mean ± SD days	80.6 ± 83.9	66.0 ± 66.0	0.17		0.32
Disease characteristics					
DAS28, mean ± SD	5.13 ± 1.26	5.78 ± 1.08	< 0.001		0.36
HAQ score, mean ± SD	0.97 ± 0.69	1.38 ± 0.64	< 0.001		0.91
Anti-CCP positive	54.7	50.0	0.51		
CRP positive	43.6	59.4	0.03		0.91
Rheumatoid factor positive	56.4	48.4	0.27		
2010 ACR/EULAR classification criteria fulfilled	83.8	85.9	0.68		
Radiographic evidence of erosion	14.0	12.5	0.77		
Psychological and behavioral factors					
MCS score, mean ± SD	39.0 ± 10.2	34.4 ± 10.7	0.002	1.05 (1.01–1.08)‡	0.005
PCS score, mean ± SD	36.9 ± 8.4	31.5 ± 7.6	< 0.001	1.07 (1.03–1.11)‡	< 0.001
Other					
Sick leave >30 days before inclusion	19.0	51.6	< 0.001	2.74 (1.37–5.47)	0.008

* Values are the percentage unless indicated otherwise. Only patients with costs >€0 were included in the analysis. Hosmer-Lemeshow goodness-of-fit test: χ^2 = 9.91, 8 df, P = 0.27, concordance index = 0.798. OR = odds ratio; 95% CI = 95% confidence interval; DAS28 = Disease Activity Score in 28 joints; HAQ = Health Assessment Questionnaire; anti-CCP = anti–cyclic citrullinated peptide antibody; CRP = C-reactive protein; ACR = American College of Rheumatology; EULAR = European League Against Rheumatism; MCS = mental component summary; PCS = physical component summary.
† OR for age is for a 10-year increase.
‡ ORs for MCS and PCS scores are for a 1-point decrease.

as extreme costs. Costs for these 64 patients represented 82% of the total costs. On multivariate analyses, older age (for a 10-year increase: OR 1.56 [95% CI 1.13–2.15], P = 0.001), a decrease in MCS and PCS scores (for a 1-point decrease: OR 1.05 [95% CI 1.01–1.08], P = 0.005 and OR 1.07 [95% CI 1.03–1.11], P < 0.001, respectively) corresponding to deteriorated mental and physical health, respectively, and sick leave due to early arthritis longer than

30 days before inclusion (OR 2.74 [95% CI 1.37–5.47], P < 0.008) were determinants of extreme costs (Table 3).

Sensitivity analyses. Sensitivity analyses of costs confirmed the robustness of the costs estimation (Table 4). The same trend was seen over the 3 years across the 5 scenarios, with a mean annual cost of approximately €1,300 per patient. Interestingly, costs did not differ between patients

Table 4. Sensitivity analyses of work productivity costs*

	1st year	2nd year	3rd year	Mean cost for 3 years	Mean cost per year
Base case†	1,562 (1,302–1,879)	1,227 (988–1,552)	1,270 (983–1,584)		
Scenario 1‡	1,502 (1,191–1,853)	1,228 (945–1,539)	1,295 (993–1,637)		
Scenario 2§	1,510 (1,210–1,879)	1,230 (967–1,533)	1,258 (958–1,604)	3,998 (3,224–4,847)	1,333 (1,075–1,620)
Scenario 3¶	1,475 (1,224–1,790)	1,255 (1,022–1,523)	1,131 (883.22–1,381.56)	3,861 (3,242–4,674)	1,287 (1,066–1,524)
Scenario 4#	1,511 (1,261–1,798)	1,194 (976–1,420)	1,237 (972–1,442)	3,942 (3,282–4,521)	1,314 (1,088–1,501)
Scenario 5**	1,537 (1,491–1,564)	1,233 (1,212–1,296)	1,294 (1,254–1,352)	4,102 (3,988–4,188)	1,351 (1,326–1,395)

* Values are the mean costs over the 3-year period (95% confidence intervals, determined by bootstrapping).
† Patients attending the followup visit (n = 579 at year 1, n = 544 at year 2, and n = 509 at year 3).
‡ Only patients fulfilling the 2010 American College of Rheumatology/European League Against Rheumatism classification criteria for rheumatoid arthritis (n = 460 at year 1, n = 443 at year 2, and n = 421 at year 3).
§ No missing followup visit over the 3 years (n = 467).
¶ Missing costs replaced by the patient's mean cost from the previous period (last observation carried forward; n = 664).
# Missing costs replaced by the mean cost of the period by sex and occupational category (n = 664).
** Multiple imputations by the Multivariate Imputation by Chained Equations procedure.

fulfilling and not fulfilling the 2010 ACR/EULAR classification criteria for RA.

Sensitivity analyses of both logistic models after multiple imputations of missing data and including all patients (n = 664) confirmed the robustness of the selected variables. In the first model, MCS and PCS scores and sick leave due to early arthritis longer than 30 days before inclusion were significantly associated with likelihood of positive costs ($P < 0.001$), but anti-CCP positivity did not have a significant impact. In the second model, age, MCS and PCS scores, and sick leave due to early arthritis longer than 30 days before inclusion were found to be significantly associated with the likelihood of extreme costs ($P < 0.001$).

DISCUSSION

The present study demonstrated that RA patients experience substantial WP loss as soon as the disease starts. Temporary sick leave from work appears to rapidly decrease, presumably due to effective therapeutic strategies. However, permanent disability in a subset of patients incurs substantial WP costs. Besides disease activity and severity, psychological and behavioral characteristics at the start of the disease appear to be important cost drivers.

Few cohort studies have evaluated work impact and its costs in early arthritis in the era of therapy with a biologic agent, and the results from this nationwide longitudinal cohort represent a broader viewpoint than economic evaluations conducted within randomized controlled trials (16–19,37,38). Importantly, the inclusion centers for ESPOIR are observational centers only, and patients may also be seen by local private rheumatologists, so patients should be highly representative of early arthritis patients. Moreover, most patients (83.3%) fulfilled the 1987 ACR criteria for RA after 2 years of disease, so these patients should be considered as having early RA.

In this study, WP loss affected less than half of patients (45%) and only 32.1% had sick leaves during the first year of disease. This result may be explained by the fact that inclusion was not limited to early arthritis patients followed in the hospital, who may have more severe disease. Comparisons with other studies of early arthritis performed in the 2000s is difficult because the recall period is often shorter and some countries quantify only sick leaves longer than 14 days, but our results seem to be lower than in other publications. Bjork et al found 33% of patients with sick leave >14 days in the previous 3 months at year 1 and Hallert et al found 62% of patients with any sick leave in the previous 6 months (14,39,40). Nevertheless, 11.2% of patients from our study declared permanent disability by the end of the third year, and this result is consistent with a 2006 French report indicating that the proportion of RA patients in France receiving disability compensations reached 10.7% after 3 years of disease (35). The sharp transition between sick leave and permanent disability over these 3 years has been noted in a few previous studies before and after the era of therapy with a biologic agent (38,41). New strategies and treatments may not be sufficient to decrease the incidence of permanent

disability. Nonetheless, this finding highlights the importance of the first years of disease in preventing job loss.

We found a mean annual indirect cost of €1,333 for patients, considering only the public payer perspective. Comparison with other studies is challenging because the health care system organization varies among countries, different perspectives are used (societal or public payer perspective), and study inclusion criteria may differ (early or established arthritis, hospital or private practice patients) (42–44). Two French studies estimated indirect costs; both were cross-sectional studies of established RA patients. The Eco-PR study conducted in 2005 found that mean annual indirect costs for 66.5% of patients ages <60 years were €2,305 from the public payer perspective (45). In a French cross-sectional multicenter cost of illness study conducted in 2000 among 1,109 hospital-based patients, the mean annual indirect cost was €2,742, but this number also included institutionalization and home service costs (46). Many studies estimating indirect costs found a wide difference between costs, from €1,297 to €22,700 (47–49). Considering the 3 studies from longitudinal cohorts of early RA patients published after 2000, indirect costs varied from €7,217 to $11,750. These studies used the human capital approach, and costs were calculated from a societal perspective, encompassing all costs regardless of the payer (13,41,50).

Univariate analysis determinants of positive and extreme WP costs in our study included disease activity and severity factors. However, only deteriorated mental and physical health and sick leave longer than 30 days before inclusion remained at multivariate analysis, which emphasizes their importance in the predictive models. Several hypotheses may be generated to explain the determinant sick leave longer than 30 days due to early arthritis before inclusion. It could be a consequence of high disease activity, but also of psychological impact, or of the influence of physicians who may easily prescribe sick leave during the early course of disease. Nevertheless, this is an important message: extended temporary sick leave as soon as the disease starts should be a "red flag" indicating imminent permanent disability. In our study, HAQ score was not a significant predictor in either model because of its correlation with PCS scores (data not shown).

Our study contains some limitations. Data were self-reported in the ESPOIR questionnaire and could not be confirmed by the National Health Insurance data. However, a previous article has shown a good correlation between reported data and official records from the National Health Insurance (51). We included only patients ages <60 years because this is the most common age of retirement in France, whereas age 65 years is more common in other settings. Costs were calculated from the public payer perspective and did not include compensation received by patients from private insurance or independent companies. Moreover, we did not evaluate lack of productivity at work (presenteeism), which can be an important part of the work impact, especially at the start of the disease, because there was no measurement scale included in the ESPOIR questionnaire (9,52).

This study focused on the impact of early arthritis on WP during the first 3 years of disease. The findings high-

light the early transition between sick leave and permanent disability and show that determinants of positive and extreme WP costs include psychological and behavioral characteristics, which should be considered by clinicians at the start of the disease to prevent job loss. Further studies of the ESPOIR cohort will be conducted over the 10 years of followup to assess the long-term burden of early arthritis and the impact of new therapies on WP.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Dadoun had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
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