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Costs of Rheumatoid Arthritis in France: A Multicenter Study of 1109 Patients Managed by Hospital-Based Rheumatologists

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ABSTRACT. ***Objective***. The economic impact of rheumatoid arthritis (RA) is substantial, but most studies provide cost estimates specific to a US population. We performed a cost-of-illness analysis of patients with RA for French society.

Methods. A cross-sectional study among rheumatologists in 148 hospitals in France was conducted between November and December 2000. Data were collected on health resource consumption associated with RA (treatments, medical devices, physician visits, examinations, hospitalization, other health professional care) during the previous 12 months. Direct costs and social costs were evaluated for 1109 RA patients. The relation of costs to disease activity and severity was analyzed.

Results. The annual direct cost of RA per patient was over €4000. The costs due to hospitalizations represented around 60% of the costs. The major reason for hospitalization was acute care for RA in a rheumatic disease ward. Patients visited a physician an average of 13 times during the 12 months, 7.7 ± 8.6 visits to an office-based physician and 5.1 ± 4.4 visits to a hospital-based physician. Among them, 37% of patients were receiving at least one disability pension (16.7%) or sick-leave allowance (11.9%), with an estimated cost of €7328 per patient. The mean annual budget per patient was €2742. Medical and social costs increased in patients with severe disease (2 times), longer disease duration since diagnosis (more than double for patients with a history longer than 10 yrs vs patients with less than 2 yrs), active disease (1.4 times), and functional status (4 times more for American College of Rheumatology class IV than for class I).

Conclusion. Direct costs represented 59% of the total costs for patients with active RA and 57% for patients with severe RA. Social costs represented 41% of the total costs on average. (J Rheumatol 2004;31:1297–304)

Key Indexing Terms:

RHEUMATOID ARTHRITIS	DIRECT COSTS	SOCIAL COSTS
DISEASE ACTIVITY	DISEASE SEVERITY	HOSPITALIZATION

Rheumatoid arthritis (RA) is a chronic disease with an overall prevalence rate of 0.31% (0.20–0.45) in a large representative population from 7 areas across France[1]. The economic impact of RA was reported to be substantial in a number of studies[2]. In a recent review by Cooper, the mean annual direct cost per patient with RA was found to be US$5720, and the mean annual indirect cost was US$5822[3].

The generalizability of RA cost estimates to the population and across countries is problematic due to the community-specific nature of the studies. Most studies have provided cost estimates specific to the US population and healthcare system. For the years 1989-91 in the US, Yelin found that the annual medical care costs of RA ranged from US$4300 to $5700 in 1994 terms in clinical settings, with hospital admissions accounting for one-half to two-thirds of the total. Indirect costs in clinical settings exceeded direct costs and ranged from just under $10,000 to more than $16,000 a year[4].

In a number of studies, medical care costs of RA are highly skewed, with persons in the 90th percentile experiencing costs more than 100 times as large as those in the 10th[4]. Patients with higher disease activity exhibited significantly higher costs compared to patients with lower disease activity[5].

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Since new biologic agents were about to enter the market in France, probably starting to dramatically modify the outcomes and the costs of the disease in a short span of time, it was considered important to document cost as a benchmark at the onset of a new era. It was also important for French society to determine the impact of RA on the patient and healthcare services. We chose a "bottom-up approach" to study all costs on an annual basis per patient. The aim of the study was to answer 3 questions: 1. What are the types of healthcare consumption for RA patients in France? 2. Based on societal perspective, what are the estimated costs of medical care (direct costs) and what are the costs of nonmedical care (social costs or transfer costs)? 3. How do the estimated costs vary with different severity levels of RA?

We estimated medical and nonmedical costs of RA within a societal perspective according to international guidelines[6,7].

MATERIALS AND METHODS

Study design. This was a cross-sectional multicenter cost-of-illness study using cross-sectional and retrospective data collection. Data were obtained from the multicenter national PRACTIS study, carried out during November and December 2000. RA patients were recruited according to the PRACTIS study design as described[8]. Participation in this study was proposed to all French hospital medical wards specializing in rheumatological diseases and based in university hospitals, public district hospitals, or nonprofit private hospitals. A mailing was sent to all centers with a department of rheumatology (Rh centers) or a department of internal medicine with a hospital-based rheumatologist (IM centers). All patients were 18 years or older and satisfied American College of Rheumatology (ACR) criteria for RA. All patients who were seen on the ward as outpatients or admitted to the hospital during the survey period were invited to participate in the study. The survey period was identical for all centers (15 days). The study was designed to capture the 12-month costs associated with RA and to identify the relationship between costs and disease severity and activity. Active disease was defined by a number of swollen joints ≥ 6 and a number of tender joints ≥ 6, and at least 2 of the following criteria: morning stiffness ≥ 45 min, C-reactive protein (CRP) ≥ 20 mg/l, erythrocyte sedimentation rate > 28 mm/h[9]. Severe disease was defined by the presence of one or more of the following: severe functional status measured by Health Assessment Questionnaire (HAQ; score ≥ 1.5); presence of typical radiological lesions; and presence of extraarticular manifestations.

Data collection. Information was collected at the day of inclusion mainly from physicians and patients and from medical records whenever necessary. Two questionnaires were administered. The first was filled in by the investigator, who noted inclusion criteria (1987 ACR criteria for RA[10]), sociodemographic variables, disease characteristics, current disease activity, ACR 1991 revised functional status[11], extraarticular manifestations, and comorbidities. Each investigator collected information on all medical and nonmedical resources consumed for RA during the preceding 12 months. Medical resources included medications for RA: disease modifying antirheumatic drugs (DMARD) consumed during the preceding 12 months and other concomitant treatments consumed during the preceding 4 weeks [analgesics, nonsteroidal antiinflammatory drugs (NSAID), antidepressive drugs, antiosteoporotic drugs, gastroduodenal protective agents]. Data on medical devices (orthopedic insoles, hand orthoses, orthopedic shoes) were collected. Medical types of care of the preceding 12 months were also recorded and included: general practitioner and specialist visits, examinations, hospital stays (number, reasons), and visits by nurses and other health professional care (physiotherapists, occupational therapists, domestic help). The second questionnaire was filled in by the patient and included the patient global assessment of disease activity, the French validated version of the HAQ, and socioeconomic data (educational status, occupation, employment status, type and amounts of allowances associated with disability, and early work retirement due to RA). The 2 questionnaires were filled in during the visit.

Cost estimates. The economic analysis was focused on quantifiable direct costs according to international recommendations[12]. The French healthcare system combines universal coverage with a public-private mix of hospital and ambulatory care. Patients have free access either to public or private health professionals, public or private hospitals, or a private office. A patient with RA can be managed by different health professionals. Usually, RA patients have an office-based rheumatologist and/or a hospital-based rheumatologist, and a referring general practitioner. Also, rheumatologists in France may work part-time at the hospital and part-time in their private office. Therefore, a multidisciplinary approach is often possible for RA patients when necessary. In this study, 2 types of costs, direct costs and social costs, were considered.

Direct cost valuation (sources of unit cost data and cost analysis). All costs were given in 2000 Euros. The exchange rate from Euro to US dollar, at the time of the study, was very close to 1 (€ 1 = US$ 1.008, January 1, 2000). Procedures and health professional fees were valued using the French nomenclature of professional fees for outpatient care[13]. Medical devices were valued using a specific price list[14]. National disease-related group cost estimates and accountability ward cost estimates from the largest public hospital organization were used for estimating hospitalization cost per day[15]. Procedures and health professional fees for inpatients were included in hospitalization costs and therefore not valued separately. Unit costs of medications were valued using the official French price list for medications[16]. Pharmaceutical costs were calculated on a patient basis using frequency or dosages and duration multiplied by unit costs. For example, for "other concomitant treatments," the data for "consumed during the preceding 4 weeks" was multiplied by 13 to obtain consumption within a 52 week period (annual costs).

Social cost valuation (sources of social cost data). Social costs included social services such as sick-leave allowances, pensions (transfer payments[12]), and home services. In the French social security system, sick leave and disability allowances are funded by several public institutions. Each has established its own rules to calculate the amount of allowances. The following types of allowances were considered: Sick-leave allowances due to RA are partly financed by the French Sickness Fund. The maximum duration of sick leave is one year, although in exceptional conditions, such as chronic diseases, sick leave can be as long as 3 years. During this period, social security insurance can allow part-time work.

- Disability allowances are also financed by the French Sickness Fund for people less than 60 years of age who worked at least 12 months before the beginning of the disabling disease.
- Extra disability allowance (AAH) may be given by the Family Allowance Fund (CAF) to people with low income according to their level of disability, family status, and income.
- Disabled people can also benefit from home care services, on physician order. Home care services consist of daily help at home (shopping, housekeeping, etc.). Home care services are paid by different institutions such as the Pension Fund, Sickness Fund, or by local authorities. An hourly cost for home care was estimated from national sources.
- A disabled patient can also be institutionalized because of their RA. The mean daily cost was estimated based on the daily cost of institutionalization according to their national distribution. Several cost items were not included due to the very low number of people affected in the sample (work status modification over the 12 month period) or lack of information (income tax reduction).

Estimation of disability costs was performed using all information collected from the patient: age, sex, disability level, family status, level of income, etc. An estimate of the amount of each allowance was calculated on a patient basis.

Statistical analysis. Descriptive statistical analysis methods were applied

for all the variables using SAS software. Cost comparisons were performed between the groups presenting with different clinical characteristics, such as ACR functional class, time from diagnosis, disease activity, and disease severity. These comparisons were performed using nonparametric tests with alpha level set at 0.05.

Sensitivity analysis was performed. The most contributive unit cost estimates into the total cost were identified, and variations of total direct cost estimates were assessed through variation of the selected unit cost estimates.

RESULTS

The inclusion period was extended from November 27 to December 8, 2000. Among all French hospital medical wards specializing in rheumatology, a total of 148 centers (86 Rh centers, 62 IM centers) were asked to participate in the study. In all, 82 centers (60 Rh centers, 22 IM centers) representing 224 physicians agreed to participate. During this period, 147 physicians from 75 centers recruited at least one patient. The mean number of investigators per center was 2.8. Among the remaining 7 participating centers who did not include patients, the mean number of investigators per center was 1.3. They were located all across France. Thirty-seven (49%) of the participating centers were based in university hospitals, 31 (41%) in public district hospitals, and 7 (9%) in nonprofit, private hospitals. A total of 1119 case report forms were collected by the investigators. In all, 1109 patient records were available for statistical analysis. Seventy percent of patients were enrolled during an outpatient visit, 9% during a day-care center visit, and 16% during a hospital stay. Enrollment situation was not mentioned for 7%.

The population included 77.3% women and 22.7% men. Mean age at inclusion was 56.7 years (± 13.9). Mean delay from diagnosis of RA was 127 months (10.6 yrs). Mean age of the patients at diagnosis was 46 years (± 15). Surgery related to RA at any time during the history of their disease was documented in 524 (47.2%) patients. Increased CRP was reported in 62.8% of the patients. Using the criteria of RA activity previously defined, 146 (13%) patients had active disease with more than 6 tender and more than 6 swollen joints, despite current treatment. Using the criteria of severity, 429 (39%) RA patients had a severe disease. Extraarticular manifestations were present in 91 patients (8.4%) at any time during disease history. Mean HAQ score was 1.32 (SD 0.77, range 0–3, median 1.25). Poor functional status was observed in 469 (43.3%) patients with a HAQ score > 1.5.

Health care consumption

DMARD and other concomitant treatments. DMARD prescribed during the previous 12 months are listed in Table 1. Other medications consumed during the previous 4 weeks were: corticosteroids (72%), NSAID (45.3%), non-morphine-based analgesics (54.7%), morphine-based agents (8%), gastroduodenal protective agents (42.5%), anti-osteoporotic treatments (36.6%), and antidepressive treatments (8%). Intraarticular injection with corticosteroids was performed an average of 1.94 times in inpatients and 2.14 times in outpatients during the previous 12 months. Other intraarticular injections (osmic acid, radioisotopes) were noted in only a few patients.

Medical visits and procedures during the previous 12 months. Patients visited a physician for RA on average 13 times during the previous 12 months, with 7.7 ± 8.6 visits to office-based physicians and 5.1 ± 4.4 visits to hospital-based physicians. An average of 8 blood tests per patient was prescribed by hospital-based physicians providing inpatient care and 34 outpatient care. An average of 2 radiographs was prescribed per patient. Other imaging procedures prescribed during the previous 12 months were ultrasonography, computed tomographic scan, magnetic resonance imaging, electromyogram, and electroretinogram (Table 2).

During the previous 12 months, 585 (53%) patients were admitted to hospital. The mean number of hospital stays per admitted patient was 2.5 ± 2.1. The median length of stay (LOS) was 7 days (1–125) and the mean LOS was 14 days per admitted patient. Surgical procedures were performed during 136 stays (9.5%). Acute treatment for RA (stays in a rheumatic ward) was the reason of hospitalization in 480 cases (33.5%). Nurse visits and other health professional care (physiotherapists, occupational therapists) are described in Table 2. Daily home care was necessary for 120 (12.6%) patients, with an average of 2.23 hours per day.

Medical devices. Orthopedic insoles and orthopedic shoes were prescribed on average once to 252 and 85 patients, respectively, during the previous 12 months. Out of the total population, hand orthoses were prescribed during a hospital stay to 119 inpatients and during an office-based visit to 111 outpatients in the previous 12 months.

Socioeconomic data. Occupation and employment status were varied. Only 304 patients were professionally active. Among these working patients, 107 patients were on sick-leave because of RA, 76 of them being on sick-leave for more than one year. An average of 178 days of sick-leave per patient concerned was reported during the past 12 months. Type and amounts of allowances associated with disability and sick leave are described in Table 3.

Cost estimates

Direct costs. Annual direct cost of RA per patient is over €4000. Mean direct cost estimates according to the type of care are presented in Table 2. The minimum amount of direct costs was €70 and the maximum amount was €47,512 (median 2021).

The most costly type of care was hospitalization. Treatments represented 13% of the medical costs, but these costs did not take into account the costs of new anti-tumor necrosis factor compounds recently introduced in France. The considerable proportion of costs due to hospitalizations,

Table 1. Disease modifying antirheumatic drugs (DMARD) consumed during the previous 12 months.

	Number of Patients (%)
Methotrexate, oral	492 (44.3)
Methotrexate, intramuscular	178 (16.1)
Methotrexate, all	638 (57.5)
D-penicillamine	25 (2.3)
Sulfasalazine	191 (17.2)
Tiopronin	50 (4.5)
Hydroxychloroquine	217 (19.6)
Intramuscular gold salts	90 (8.1)
Oral gold salts	15 (1.4)
Azathioprine	21 (1.9)
Cyclophosphamide	14 (1.3)
Cyclosporine	59 (5.3)
Other treatments [anti-TNF, leflunomide, anti-CD4]	257 (23.2)
All DMARD	999 (90.1)

which represented around 60% of the costs, had a marked effect on the corresponding unit cost estimate. A variation of 30% of the daily cost in a rheumatic ward led to a 10% variation in total direct costs estimates.

Social costs

Thirty-seven percent of the patients (n = 415) were receiving at least one disability or sick-leave allowance. The mean amount was estimated at €7328 per recipient patient and mean annual amount per included patient was €2742. Results by categories of costs are listed in Table 3. The minimum amount of social costs for recipient patients was €22 and the maximum amount was €28,342 (median 5658).

Economic analysis according to clinical variables

Comparisons between patients presenting with different clinical characteristics (Table 4) showed that medical and

Table 2. Direct costs (€ 2000) and healthcare consumption during the previous 12 months.

Type of Care	Hospitalized Care	Ambulatory Care	Costs (SD) [2000 Euro]	% of Total
Physician visits for RA, mean (SD)			263 (191)	7
Rheumatologists	4.49 (3.25)	5.86 (4.32)		
General practitioners	6.76 (4.22)	8.50 (7.10)		
Other specialists	2.05 (1.56)	2.43 (4.11)		
Exams for RA, mean (SD)			448 (304)	11
Blood tests	7.7 (14.2)	33.8 (23.1)		
Radiographs	2.0 (3.0)	1.2 (2.0)		
Other imaging procedures	0.5 (1.2)	0.4 (0.8)		
Other health professional and medical encounters, mean (SD)			361 (797)	9
Nurse visits	16.9 (67.5)	35.2 (65.7)		
Physiotherapist	22.2 (39.6)	39.6 (50.6)		
Occupational therapist	10.2 (21.2)	9.9 (14.4)		
Medical devices	—	1.13 (0.45)		
Hospitalization			2430 (4803)	60
No. of patients admitted	585			
No. of hospital stays per patient admitted, mean (SD)	2.4 (2.1)			
Length of stay, days, mean (SD)	14.1 (19.8)			
Medication, mean (SD)			500 (1817)	13
Total direct costs, mean (SD)			4003 (5340)	100

* Examinations include laboratory tests for disease or drug monitoring and imaging procedures (in ambulatory care).

Table 3. Mean annual social costs (disability and sick-leave allowances) per patient (2000 Euro)

Type of Cost	Mean Annual Costs per Patient (n = 1109)	No. of Recipient Patients	Mean Annual Costs per Recipient Patient
Disability allowance	949	186	5659
Special disability fund	130	23	6276
Adult disability scheme	408	82	5512
Extra adult disability scheme	34	35	1070
Home services	482	120	4458
Sick-leave allowance	513	132	4308
Institutionalization	226	11	22835
Total disability and sick-leave allowances (2000 Euros)	2742	415*	7328

* Received at least one.

societal costs increased with severity, duration since diagnosis, and activity and functional status. Table 4 shows that the total direct costs per patient increased as the ACR functional classes worsened. The amount was almost the same in class I and II, and increased from 2 to 3-fold in patients with ACR class III and IV, respectively. A significant difference was also observed between the 4 ACR classes for mean social costs (mean disability and sick leave allowances) per included patients. With regard to the duration of the disease, the social costs were higher for those patients with RA for more than 10 years. The mean costs of RA per patient included were also significantly associated with disease severity and disease activity. Total costs for patients with severe RA were evaluated to almost twice the costs for patients with a non-severe RA ($p < 0.001$).

DISCUSSION

This is the first large study conducted in France to evaluate healthcare consumption and associated costs of RA. Since RA patients were recruited from across the country, the sample is representative of the RA population managed by hospital physicians. Patient characteristics were similar to other cost-of-illness studies. The proportion of women of 77.3%, mean age of 56.7 years, and mean duration of disease of 10.6 years were comparable to those of other cost-of-illness studies. The mean level of functional disability measured by the HAQ ranged from 0.96 to 1.53 in previous studies, versus a mean of 1.32 (± 0.77) in our study. In a previous French study, Sany, *et al* identified major resources consumed by 1629 patients with RA who were managed by non-hospital-based rheumatologists[8]. Compared to our results, healthcare consumption was different: only 35% of patients were admitted to the hospital during the previous 2 years. The number of visits to physicians was also lower, with a median of 5 visits per year. DMARD were prescribed to 84% of patients, and 52% had oral steroids at the time of inclusion. Lower disability scores were also observed: 74% of the patients were Steinbrocker class I and II. Therefore, we thought that healthcare use and costs of RA in patients managed by private-practice rheumatologists may be quite different than patients managed by hospital-based rheumatologists. Our goal was to better analyze the direct and the social costs with a correlation to disease characteristics.

In our study, direct medical cost calculations were based upon healthcare consumption including hospitalizations, physician visits, medications, medical devices, laboratory tests, and surgical procedures during the preceding 12 months. Items such as transportation to and from the doctor were not included. We included home services (nonmedical cost) in the social cost estimates. Annual direct costs were calculated to an average of €4003 per patient per year. The major component of this cost was hospitalization, representing 60% of the direct costs, while costs of medication represented a comparatively small proportion of direct costs. This is in accord with international literature, although costs of new medications were not considered.

In a review of the international literature over 15 years ago, Lubeck found that the mean annual resource consumption averaged almost US$7000 for a patient with RA[3,17]. For most studies, inpatient costs (i.e., hospitalizations) were found to be the largest component of the total annual medical costs associated with RA[3,17]. According to Pugner, *et al*[12] the percentage of hospitalization contributing to total direct costs, evaluated over a 20 year period in different US and European studies, was from 16% to 67%, with a median of 47%. In the one-year period 1995-96, hospitalization for RA represented 51.7% of the total medical care costs, and

Table 4. Costs according to functional class, duration since diagnosis, and activity and severity of RA (2000 Euro).

Clinical Variables	No. of Patients	Mean Direct Costs, €	Mean Disability and Sick-leave Allowances, €
ACR functional class*		*p < 0.001*	*p < 0.001*
I	207	2233	930
II	305	2888	1964
III	338	4099	3463
IV	251	6748	4171
Duration since diagnosis*, yrs		*p = 0.007*	*p < 0.001*
< 2	178	3735	1518
2–10	436	3429	2513
> 10	482	4573	3323
Activity†		*p < 0.001*	*p = 0.025*
Active	146	5402	3699
Not active	963	3791	2597
Severity†		*p < 0.001*	*p < 0.001*
Severe	429	5797	4218
Not severe	680	2871	1811

* Kruskall and Wallis test; † Mann and Whitney test.

total joint replacement accounted for half the hospital costs. Medical admissions were more than 10 times less costly than surgery for RA[18]. In our study, hospitalizations during the previous 12 months were mostly for medical reasons, while surgery was less frequent. Therefore, the major part of the direct costs was represented by the medical care of RA.

This difference could be explained by a different type of care in France due to health services, physician practice patterns in RA, or a decrease in the need for surgery in RA. In a prospective pilot study conducted in France, 20 incident cases of RA were evaluated during a 6 month period on a day-hospital basis[19]. Mean total cost for the 6-month period was €3429 ± 880. Laboratory tests contributed the largest portion of the total cost (39%), followed by rheumatologist care (16%). The other costs accounted for 7.6 to 9.2% of the total cost[19].

The use of healthcare by RA patients and the factors determining their patterns of healthcare use were also recently analyzed in a multicenter European cohort of 223 RA patients compared to 446 nonarthritic subjects[20]. It was found that medication use was reported in 92.3% of the RA patients. Hospitalization in the past 12 months was reported by 39.2% of RA patients versus 12.6% of nonarthritic patients ($p < 0.001$). The number of contacts with a general practitioner and specialists were, respectively, 7.1 and 12.4 in RA patients, which was significantly more than in nonarthritic patients. RA patients had more contacts with medical and social health professionals[20]. Such comparisons usefully highlight the excess cost attributable to RA.

Direct costs were also significantly correlated with disease severity and ACR functional class in our study. This is in accord with other cost-of-illness studies. According to Yelin and Wanke's RA panel study of 1156 patients, persons with RA in the worst quartile of function experienced total annual direct costs that were 2.55 times as high and total hospital costs that were 6.97 times as high as those in the best (e.g., the first) quartile[18]. A recent Italian study of 200 RA patients found that direct costs increased very significantly among the 4 functional classes, as did indirect costs[21].

Social costs represented a large part of the total costs in our study. In France, the social security system allows for different levels of disability, from low level to higher level allowances. Therefore, a large number of RA patients receive disability allowances. Social costs (and transfer payments) are usually considered as part of direct costs, but these costs also represent days where patients are absent from work, and may be included in evaluation of indirect costs. In our results, among working patients, 107 patients were on sick leave because of RA, with 76 of them on leave for more than one year. An average of 178 days of sick leave per patient concerned was reported during the previous 12 months. In cost-of-illness studies where indirect costs were considered, it was usually included as the number of days absent from work per year due to RA. According to Cooper, these ranged from 2.7 days/year to 30 days/year per employed patient[3]. The mean annual indirect cost calculated by Cooper was US$5822 (1996 US$).

Although in agreement that indirect costs far exceed direct costs, Cooper found that 50% of the studies that estimated both direct and indirect costs reported direct costs to be the largest contributor of total costs[22]. Two studies reported indirect costs to be about double the direct costs, although using different economic perspectives[22,23]. In these studies, patients with higher indirect costs had a more severe disease, with anatomic stage III RA[23]. In our study, social costs were estimated to be half the medical direct costs but included only the transfer costs. Another study performed in Germany analyzed the indirect costs of 133 patients with early RA who were employed at the time of RA onset. Over 2 year followup, an average of 82 days of sick leave per person-year was reported, accounting for a mean annual cost of US$7640. In this study, high indirect annual costs were identified even in the early phase of RA[24]. A British study estimated the 6 month total costs of 133 individuals with early inflammatory arthritis. The largest proportion of costs incurred by the health service was for inpatient stays and day-unit visits, and the mean costs increased with the HAQ score. Only 14% of the total costs were incurred by the health service and the remaining 86% were non-healthcare costs[25].

In our analysis, we compared the total costs between different clinical variables in patients with RA (Table 4) using nonparametric tests. As we expected, the total costs were correlated to the duration of RA and to the ACR functional status of RA. In a longterm study of mortality, morbidity, and economics in RA involving 4258 consecutively enrolled RA patients followed up for 17,085 patient-years, lifetime direct medical care costs were estimated to be US$93,296. Higher costs were associated with higher disability scores[26]. Other economic studies using different simulation models also showed that the costs increased with increasing severity of disease over a 5 to 15 year period[27,28]. In a Swedish study, total costs over 5 years were higher for patients in more severe condition at diagnosis[28]. Other studies showed a correlation between costs and duration of RA, especially when costs to the patient, rather than to the healthcare system, were considered. In a prospective study of 81 patients, women were more affected by RA than men in health status, social impact, and out-of-pocket costs, including nonprescription medication, assistive devices, and changes in their living arrangements because of RA[29].

Our study was hospital-based, and the results should be interpreted with caution as the RA patients probably had more severe disease than patients from a community-based cohort. Although it is difficult to compare 2 types of study settings, we collected information from community-based[25,30] versus hospital-based cost-of-illness studies[21-33] (Table 5). In the few published community-based cost-of-

Table 5. Mean costs per patient for rheumatoid arthritis by country.

	United Kingdom, 2002[25]	USA, 1997[28]	USA, 2003[31]	Germany, 2003[32]	France, 2004 Current Study	Spain, 2003[33]	Italy, 2002[21]
No. of patients	133	365	7527	338	1109	201	200
Type of setting	Community	Community (HMO)	Community	Community	Hospital	Hospital	Hospital
Time of study	1994–1999	1993–1994	1999–2001	2000–2001	1999–2000		1998
Currency	£ 1998–99	US Dollar	2001 USD	Euro	2000 Euro	2001 USD	Euro
Mean total annual cost per patient	2791 (2080–3713)	2162	9519	3815	6745	10419	3718.3–22946.0 [class I–class IV]
Direct costs	385 (14% of total) (235–638)	2162	9519	2312	4003	70% of total	1643.4–5696.8 [class I–class IV]
Inpatient costs (hospitalization)		356 (16%)	1573 (17% of total)	24%	2430		399.6–1968.5
Outpatient costs			6324 (66% of total)	73.7%			558.1–1102.7
Drugs		1342 (62%)		1019	500		
Physician visits		264		323	263		
Tests		86		185	448		
Devices and aids				168	361 (+ other HP)		
Social costs					2742		
Sick-leave				2835	513		
Work disability payment				8358	2229		
Indirect costs	86% of toal	NC	NC	NC	NC	30% of total	2704.9–17249.2 [class I–class IV]
Patients on biologic therapy			25%				

NC: not calculated; other HP: other health professionals; HMO: health management organizations.

illness studies, findings usually show that total costs were lower for community-based RA patients than for those managed in a hospital setting. Differences can stem from differences between countries in treatment practices and social care programs. In France, the healthcare system combines universal coverage with a public-private mix of hospital and ambulatory care. Patients can be managed in public or private hospitals or in a private office or both. Therefore, when necessary, a multidisciplinary approach is often possible for RA patients in France. This fact could limit the bias of the comparison between hospital-based and community-based management. Nevertheless, this approach will probably change with the prescription of biologic treatments earlier in the disease course[31,32].

In conclusion, this first cross-sectional and multicenter study of costs of RA managed by hospital-based rheumatologists conducted in France provides extensive descriptive data on healthcare use and shows that medical costs and social costs are substantial in patients with RA, and that higher costs are associated with a higher severity and activity of RA. Knowledge of cost distribution leads to better use of healthcare consumption. Aletaha, et al recently showed that costs of monitoring drug therapy could probably be reduced by using evidence-based recommendations for routine laboratory tests[34]. Considering the total costs of RA may also help rheumatologists choose new disease modifying antirheumatic drugs for patients with moderate to severe disease activity/severity presentation[35].

Future research is needed to analyze the impact of new management strategies on RA aimed at reducing the severity and probably the costs of the disease[36,37]. New biological therapy could change the overall aspects of disease severity and therefore decrease longterm costs of RA[37]. Additional prospective observational and pharmaco-economic studies using our data for benchmarking are necessary to validate this hypothesis.

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REFERENCES

1. Guillemin F, Saraux A, Guggenbuhl P, et al. Prévalence de la polyarthrite rhumatoïde et des spondylarthropathies en France en 2001. Rev Rhum Mal Osteoartic 2002;69:1014-38.
2. Fautrel B, Guillemin F. Cost of illness studies in rheumatic diseases. Curr Opin Rheumatol 2002;14:121-6.
3. Cooper NJ. Economic burden of rheumatoid arthritis: a systematic review. Rheumatology 2000;39:28-33.
4. Yelin E. The costs of rheumatoid arthritis: absolute, incremental, and marginal estimates. J Rheumatol 1996;23 Suppl 44:47-51.
5. Van Jaarsveld CH, Jacobs JW, Schrijvers AJ, Heurkens AH, Haanen HC, Bijlsma W. Direct cost of rheumatoid arthritis during the first six years: a cost-of-illness study. Br J Rheumatol 1998;37:837-47.
6. Gabriel S, Tugwell T, O'Brien B, et al. Report of the OMERACT Task Force on Economic Evaluation. J Rheumatol 1999;26:203-6.
7. Gabriel SE, Tugwell P, Drummond M. Progress towards an OMERACT-ILAR guideline for economic evaluations in rheumatology. Ann Rheum Dis 2002;61:370-3.
8. Sany J, Bourgeois P, Saraux A, et al. Characteristics of patients with rheumatoid arthritis (RA) in France: a study of 1109 patients managed by hospital-based rheumatologists. Ann Rheum Dis 2003;62:S67
9. Felson D, Anderson J, Boers M, et al. The American College of Rheumatology preliminary core set of disease activity measures for rheumatoid arthritis clinical trials. Arthritis Rheum 1993;36:729-4.
10. Arnett FC, Edworthy SM, Bloch DA, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988;31:315-24.
11. Hochberg MC, Chang RW, Dwosh I, Lindsey S, Pincus T, Wolfe F. The American College of Rheumatology 1991 revised criteria for the classification of global functional status in rheumatoid arthritis. Arthritis Rheum 1992;35:498-502.
12. Pugner KM, Scott DI, Holmes JW, Hieke K. The costs of rheumatoid arthritis: an international long-term view. Semin Arthritis Rheum 2000;29:305-20.
13. Union des Caisses Nationales de Sécurité Sociale. Nomenclature Générale des actes professionnels. Paris: UCANSS; 2000.
14. Union des Caisses Nationales de Sécurité Sociale. Nomenclature Générale des actes professionnels. Tarif Interministériel des Prestations Sanitaires. Paris: UCANSS; 2000-2001.
15. Base Nationale PMSI 1999/Echelle Nationale de coût en point ISA – Direction des Hôpitaux, Ministère du Travail, de l'Emploi et de la Solidarité. [Internet]. 2001 [Cited March 3, 2004]. Available from: www.le-pmsi.org/mco/infos/plfss2001.html
16. Le dictionnaire Vidal. Issy les Moulineaux, France: Vidal: 2000.
17. Lubeck DP. A review of the direct costs of rheumatoid arthritis. Managed care versus fee-for-service settings. Pharmacoeconomics 2001;19:811-8.
18. Yelin E, Wanke LA. An assessment of the annual and long-term direct costs of rheumatoid arthritis: the impact of poor function and functional decline. Arthritis Rheum 1999;42:1209-18.
19. Maravic M, Bozonnat MC, Sevezan A, et al. Preliminary evaluation of medical outcomes (including quality of life) and costs in incident RA cases receiving hospital-based multidisciplinary management. Joint Bone Spine 2000;67:425-33.
20. Girard F, Guillemin F, Novella JL, et al. Health-care use by rheumatoid arthritis patients compared with non-arthritic subjects. Rheumatology Oxford 2002;41:167-75.
21. Leardini G, Salaffi F, Montanelli R, Gerzeli S, Canesi B. A multicenter cost-of-illness study on rheumatoid arthritis in Italy. Clin Exp Rheumatol 2002;20:505-15.
22. Stone CE. The lifetime economic costs of rheumatoid arthritis. J Rheumatol 1984;11:819-27.
23. Meenan RF, Yelin EH, Henke CJ, Curtis DL, Epstein W. The costs of rheumatoid arthritis. A patient oriented study of chronic disease costs. Arthritis Rheum 1978;21:827-33.
24. Merkesdal S, Ruof J, Schoffski O, Bernitt K, Zeidler H, Mau W. Indirect medical costs in early rheumatoid arthritis. Arthritis Rheum 2001;44:528-34.
25. Cooper NJ, Mugford M, Symmons DP, Barrett EM, Scott DG. Total costs and predictors of costs in individuals with early inflammatory polyarthritis: a community-based prospective study. Rheumatology Oxford 2002;41:767-74.
26. Wong JB, Ramey DR, Singh G. Long-term morbidity, mortality, and economics of rheumatoid arthritis. Arthritis Rheum 2001;44:2746-9.
27. Kobelt G, Jonsson L, Lindgren P, Young A, Eberhardt K. Modeling the progression of rheumatoid arthritis: a two-country model to estimate costs and consequences of rheumatoid arthritis. Arthritis Rheum 2002;46:2310-9.
28. Kobelt G, Eberhardt K, Jonsson L, Jonsson B. Economic consequences of the progression of rheumatoid arthritis in Sweden. Arthritis Rheum 1999;42:347-56.
29. Lapsley HM, March LM, Tribe KL, Cross MJ, Courtenay BG, Brooks PM; Arthritis Cost and Outcome Project Group. Living with rheumatoid arthritis: expenditures, health status, and social impact on patients. Ann Rheum Dis 2002;61:818-21.
30. Lanes SF, Lanza LL, Radensky PW, et al. Resource utilization and cost of care for rheumatoid arthritis and osteoarthritis in a managed care setting: the importance of drug and surgery costs. Arthritis Rheum 1997;40:1475-81.
31. Michaud K, Messer J, Choi HK, Wolfe F. Direct medical costs and their predictors in patients with rheumatoid arthritis: a three-year study of 7,527 patients. Arthritis Rheum 2003;48:2750-62.
32. Ruof J, Hulsemann JL, Mittendorf T, et al. Costs of rheumatoid arthritis in Germany: a micro-costing approach based on healthcare payer's data sources. Ann Rheum Dis 2003;62:544-9.
33. Lajas C, Abasolo L, Bellajdel B, et al. Costs and predictors of costs in rheumatoid arthritis: a prevalence-based study. Arthritis Rheum 2003;49:64-70.
34. Aletaha D, Smolen JS. Laboratory testing in rheumatoid arthritis patients taking disease-modifying antirheumatic drugs: clinical evaluation and cost analysis. Arthritis Rheum 2002;47:181-8.
35. Erkan D, Yazici Y, Harrison MJ, Paget SA. Physician treatment preferences in rheumatoid arthritis of differing disease severity and activity: the impact of cost on first-line therapy. Arthritis Rheum 2002;47:285-90.
36. Nuijten MJ, Engelfriet P, Duijn K, Bruijn G, Wierz D, Koopmanschap M. A cost-cost study comparing etanercept with infliximab in rheumatoid arthritis. Pharmacoeconomics 2001;19:1051-64.
37. Wong JB, Singh G, Kavanaugh A. Estimating the cost-effectiveness of 54 weeks of infliximab for rheumatoid arthritis. Am J Med 2002;113:400-8.