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Direct Medical Costs and Their Predictors in Patients With Rheumatoid Arthritis

A Three-Year Study of 7,527 Patients

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Objective. **To estimate total direct medical costs in persons with rheumatoid arthritis (RA) and to characterize predictors of these costs.**

Methods. **Patients (n = 7,527) participating in a longitudinal study of outcome in RA completed 25,050 semiannual questionnaires from January 1999 through December 2001. From these we determined direct medical care costs converted to 2001 US dollars using the consumer price index. We used generalized estimating equations to examine potential predictors of the costs. Monte Carlo simulations and sensitivity analyses were performed to evaluate the varying prevalence and cost of biologic therapy.**

Results. **The mean total annual direct medical care cost in 2001 for a patient with RA was $9,519. Drug costs were $6,324 (66% of the total), while hospitalization costs were only $1,573 (17%). Approximately 25% of patients received biologic therapy. The mean total annual direct cost for patients receiving biologic agents was $19,016 per year, while the cost for those not receiving biologic therapy was $6,164. RA patients who were in the worst quartile of functional status, as measured by the Health Assessment Questionnaire, experienced direct medical costs for the subsequent year that were $5,022 more than the costs incurred by those in the best quartile. Physical status as determined by the Short Form 36 physical component scale had a similar large effect on RA costs, as did comorbidity. Medical insurance type played a more limited role. However, those without insurance had substantially lower service utilization and costs, and health maintenance organization patients had lower drug costs and total medical costs. Increased years of education, increased income, and majority ethnic status were all associated with increased drug costs but not hospitalization costs. Costs in all categories decreased after age 65 years.**

Conclusion. **Estimates of direct medical costs for patients with RA are substantially higher than cost estimates before the biologic therapy era, and costs are now driven predominantly by the cost of drugs, primarily biologic agents. RA patients with poor function continue to incur substantially higher costs, as do those with comorbid conditions, and sociodemographic characteristics also play an important role in determination of costs.**

The costs of rheumatoid arthritis (RA) are increasing because of the introduction and increasing use of biologic therapy. Biologic agents are effective but expensive, and there are almost no data to measure their impact on costs among RA patients in the community. In a sense, with the introduction of biologic therapy everything is new: RA costs have to be measured all over again to account for these agents. Additionally, costs are a changing target; if the prevalence of biologic therapy use increases, costs estimated today or in the past (1–14) may not be valid after a few years.

Lubeck (1) reviewed 10 studies on the costs of

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RA and noted that hospitalization costs were generally ≥60% of direct medical costs, with a single exception (9), and that drug costs were <25% of total direct medical costs. Pugner et al (15) reviewed cost studies (2–10) performed between 1978 and1998. They reported that the mean annual direct cost of RA was $5,425 per patient when expressed in 1998 US dollars. The median percentage of costs attributed to hospitalization in their review was 47%, and the percentage attributed to drugs was 16%. Gabriel and colleagues reported average annual direct medical charges to be $3,802 in 357 patients with RA and $2,654 in 5,730 patients with osteoarthritis (13); a random subset of patients was used to estimate charges for prescription medications in that study. Newhall-Perry et al studied the costs of RA in 150 seropositive patients during the first 5 years of illness and found the average total cost of the disease to be $2,400 per year (11). Lanes and colleagues reported on RA costs among health maintenance organization (HMO) patients from 1993 to 1994 (9). The average annual costs were $2,162, and 16% of the costs were for hospitalization. The study by Lanes et al is the only previous study in which drug costs were found to be the predominant cost in RA.

The study that is perhaps most germane to the current report is that by Yelin and Wanke (12). In 1999, they reported on 272 patients who were followed up continuously in 1995 and 1996. The average annual direct medical costs from a societal perspective were $8,501. Drugs constituted 18.2% and hospitalization accounted for 61.8% of total costs. The authors point out that hospital charges in California for that study may not be representative of hospital costs generally, and they prepared a second set of estimates based on a discount of 50% for hospital costs; this was discussed in their text though not included in the statistical tables. Applying the 50% discount would reduce the total cost from $8,501 to $5,876; both numbers are relevant in comparing the current report with the data of Yelin and Wanke.

Herein we describe the direct medical costs for persons with RA, encompassing costs no matter who incurs them (societal perspective), and identify predictors of these costs. We report that drugs are the predominant cost factor in RA, and that total costs are considerably greater than in studies performed prior to the introduction of biologic agents. In addition, we report the quantitative effect of a wide variety of predictors on future costs.

PATIENTS AND METHODS

Patient population. This study was performed using the National Data Bank for Rheumatic Diseases (NDB). The NDB is a rheumatic disease research data bank in which patients complete detailed self-report questionnaires at 6-month intervals. The characteristics of the NDB have been reported previously (16–18). Patients in the NDB are recruited from 2 sources: 1) nonselected patients from the practices of US rheumatologists, and 2) patients enrolled as part of pharmaceutical company–sponsored registries. Eligible patients in this study were those with RA who had completed at least 2 of 6 possible semiannual surveys for events between January 1, 1999 and December 31, 2001. All patients who were recruited as part of pharmaceutical company registries were excluded, to avoid possible bias. The resultant data set contained 7,527 RA patients and 25,050 observations from the 3-year period. Patients were referred by 233 rheumatologists dispersed throughout the US. More than 90% of the rheumatologists were in private practice and were not full-time university physicians. The diagnosis of RA was made by the patients' rheumatologists.

Demographic and disease status variables. NDB participants were asked to complete semiannual, detailed 28-page questionnaires about all aspects of their illness. At each assessment, demographic variables were recorded, including sex, age, ethnic origin, education level, current marital status, medical history, and total family income. Disease status and activity variables collected included the Stanford Health Assessment Questionnaire (HAQ) functional disability index (19,20), pain, global disease severity, and fatigue as recorded on visual analog scales (VAS) (21), the Arthritis Impact Measurement Scales (AIMS) anxiety and depression scales (22,23), and the Rheumatoid Arthritis Disease Activity Index (RADAI) (24–26). Patients also completed the Medical Outcomes Study Short Form 36 (SF-36), from which the physical component score (PCS) and the mental component score were calculated (27,28). Utilities were mapped from HAQ, anxiety, and depression values, based on a regression model derived from the simultaneous administration of the EuroQol (29–31), HAQ, and anxiety and depression scales to 2,299 RA patients (32). We also used the SF-36–derived utility index, the SF-6D (33). The comorbidity score represented the sum of 11 comorbid conditions, as reported previously (34).

Patients also completed several instruments measuring productivity, the number of days they were unable to perform their usual activities in the last 30 days, the number of days they were unable to work in the last 180 days, and the Work Limitations Questionnaire (35,36). In addition, patients reported on the number of persons they depended on for help and whether help was needed none, a little, some, most, or all of the time.

Direct medical costs. Direct medical costs in this study include expenditures for physician and health care worker visits, medications, diagnostic tests and procedures, and hospitalizations. In the study surveys, patients reported all drug use, hospitalizations, medical visits, procedures, and laboratory testing. Medical costs reflected both RA and non-RA direct costs. Drug costs were assigned using Center for Medicare and Medicaid Services (CMS; the organization succeeding the Health Care Financing Administration) (37), Federal Upper

Limit, or wholesale rates according to *Drug Topics Red Book* (38). We requested copies of hospital and procedure records for all hospitalizations, and obtained diagnosis-related group (DRG) and procedure codes from the records. In the event records could not be obtained, we imputed DRG and procedure codes based on patients' reported events. Hospitalizations were assigned costs according to their DRG classification using national values from CMS's Medicare Provider Analysis and Review (37) and were adjusted by the number of days of inpatient care. In addition, average hospitalization physician fees were added depending on whether the stay was for medical ($500) or surgical ($2,000) services. Laboratory costs were derived from Medicare utilization tapes for patients with RA and applied to study patients with laboratory usage, since we could not always accurately determine the number and specific kinds of laboratory tests from a patient's self-report.

Cost data for procedures, medical visits, and laboratory services were obtained from the Medicare Physician Fee Schedule, with outpatient procedure costs modified by the national Medicare utilization rates. For example, typical cost estimates used in this report for events in the year 2000 were as follows: average physician visit codes (CPT 99211–99215) $49.50, hand and wrist radiograph (CPT 73100) $27.54, hip radiograph (CPT 73500) $27.19, gall bladder procedures (includes 52 CPTs) $688, and hospitalization for conditions involving major joints of the lower extremity, 5.2-day stay (DRG 219) $9,254 and 3.2 day stay (DRG 209) $4,083.

All costs were initially calculated using the above resources for the appropriate year of patient observation. Costs were then inflation-adjusted to 2001 US dollar rates using the consumer price index from the Bureau of Labor Statistics (www.bls.gov). Costs in this study are reported per 6 months, reflecting the semiannual survey data, except as specifically described. A time-trend dummy variable (calendar half-year) was included in the analyses to reflect the particular 6-month survey period.

In calculating infliximab costs, we assumed that infliximab was being administered at a dose of 3 mg/kg (227.7 mg for an average measured weight of 75.9 kg per infliximab user), but we rounded up the dose to make use of the full vial of infliximab. The average dose/kg that made use of 3 vials (300 mg), therefore, was 3.96 mg/kg. This is closely consistent with postmarketing data supplied to the authors by Centocor, Inc., after this study was completed, that indicated that the mean infliximab dose in 150 patients was 3.98 mg/kg during 2001 and 2002. At a dose of 5 mg/kg (379.5 mg), the number of vials required would be 4 (400 mg). This would result in an increase in infliximab costs of 25%.

For this report we chose to include all medical costs, not just RA costs, because it is not always clear what is an RA cost. Over the last few years cardiovascular disease and other illnesses such as infections and gastrointestinal ulcers have been recognized as potential consequences of RA (39–42). In addition, many patients receive their RA and non-RA care from general physicians, and it is not possible to disaggregate such costs into RA and non-RA components. Another issue of importance is the term "costs," as opposed to the term "charges." In the current report we have used the term "costs" because we relied on cost payment figures from Medicare sources and used minimum cost estimates for drugs. This difference between costs and charges is the reason we used the 50% discount for the Yelin and Wanke study (12), so relatively comparable estimates would be available.

Table 1. Clinical and demographic characteristics of the 7,527 RA patients at their most recent survey*

Age, years	61.7 ± 13.1 (62.6)
Sex, % male	23.2
Education, years	13.5 ± 2.3 (13)
Highest year of education, %	
0–8	2.3
8–11	7.6
12	36.7
13–15	25.7
≥16	27.6
Ethnicity, %	
Non-Hispanic white	92.4
African American	3.2
Asian American	1.1
Native American	0.9
Mexican/Mexican American	1.9
Puerto Rican	0.1
Other	0.4
Total income, US dollars × 10,000	4.5 ± 2.9 (3.5)
Lifetime comorbidity score, 0–11	2.7 ± 1.9 (2)
Disease duration, years	15.0 ± 11.1 (11.9)
HAQ score, 0–3	1.05 ± 0.74 (1)
RADAI score, 0–10	3.3 ± 2.1 (3.1)
Pain score, 0–10	3.7 ± 2.7 (3)
Global severity score, 0–10	3.4 ± 2.5 (3)
Fatigue score, 0–10	4.2 ± 2.9 (4)
Depression score, 0–10	2.3 ± 1.7 (2.0)
SF-36 physical component score	32.4 ± 10.4 (31.4)
SF-36 mental component score	44.4 ± 14.1 (47.3)
VAS QOL scale, 0–100	69.0 ± 20.3 (75)
EuroQol utility, 0–1	0.64 ± 0.21 (0.67)
SF-6D utility, 0–1	0.63 ± 0.10 (0.61)

* Except where indicated otherwise, values are the mean ± SD (median). RA = rheumatoid arthritis; HAQ = Health Assessment Questionnaire; RADAI = Rheumatoid Arthritis Disease Activity Index; SF-36 = Short Form 36; VAS = visual analog scale; QOL = quality of life; SF-6D = SF-36–derived utility index.

To understand the relationship between drug therapy and medical insurance coverage, we added a question to the last survey of 2001, asking about the extent to which RA patients have to pay for their medications out of pocket, as opposed to having insurance pay for the medications. We then organized patient responses according to whether they had to pay ≥25%, as opposed to having to pay <25%, of their drug costs; 20.1% of the participants did not answer this question.

Statistical methods. To determine the effect of previous disease status and activity on current medical costs, "lagged" predictor variables were created for the HAQ, RADAI, depression, fatigue, comorbidity, utilities, and PCS. A lagged variable represents the value of the study variable (e.g., HAQ) in the assessment 6 months prior to the current assessment.

Graphic analysis of the effect of age on total direct costs indicated an inverted V-shaped nonlinear relationship, with a relatively linear positive component from age 15 years through age 65 years and a linear negative component after that age. To model these separate components of age, linear splines were created. Linear splines allow estimation of the

Table 2. 2001 direct annual medical costs for 7,527 RA patients, by cost type*

Cost type	Cost, $ (95% CI)	% (95% CI)
Outpatient costs, total	1,541 (1,501, 1,581)	16.2 (15.4, 17.0)
Physician and health professional	674 (662, 686)	7.1 (6.8, 7.4)
Radiographs	329 (311, 347)	3.5 (3.2, 3.7)
MRI, CT scans	199 (185, 212)	2.1 (1.9, 2.3)
Endoscopies	93 (86, 99)	1.0 (0.9, 1.1)
Other tests†	130 (126, 134)	1.4 (1.3, 1.4)
Outpatient surgery	114 (106, 123)	1.2 (1.1, 1.3)
Drug costs, total	6,324 (6,172, 6,477)	66.4 (63.4, 69.6)
DMARDs	643 (619, 667)	6.8 (6.4, 7.2)
Biologic agents	3,307 (3,164, 3,451)	34.7 (32.5, 37.1)
NSAIDs	591 (573, 610)	6.2 (5.9, 6.6)
GI medications and analgesics	518 (496, 540)	5.4 (5.1, 5.8)
Non-RA medications	1,247 (1,224, 1,270)	13.1 (12.6, 13.7)
Hospitalization costs, total	1,573 (1,450, 1,697)	16.5 (14.9, 18.2)
Total costs	9,519 (9,301, 9,737)	100

* Adjusted for age, sex, and calendar half-year. RA = rheumatoid arthritis; 95% CI = 95% confidence interval; MRI = magnetic resonance imaging; CT = computed tomography; DMARDs = disease-modifying antirheumatic drugs; NSAIDs = nonsteroidal antiinflammatory drugs; GI = gastrointestinal.
† Includes laboratory tests, Doppler examinations, treadmill tests, mammograms, bone density tests, and other examinations.

relationship between y and x variables as a piecewise linear function in which one segment represents (in this instance) the values below age 65 years and the other segment the values above age 65 years (43). A nonlinear relationship was also noted for disease duration, with turning points at 10 years and 40 years. Splines were formed to describe this relationship. Subsequent analyses indicated that the relationship between the third spline (>40 years) and costs was not significant. Because of nonsignificance and the relatively small number of patients with disease duration >40 years, we reverted to a 2-spline basis with a single cut point (knot) at 10 years.

The relationships between costs and predictor variables were analyzed with a generalized estimating equation (GEE) procedure. Stata's implementation of the GEE procedure (XTGEE) is an extension of generalized linear models that properly handle panel data (43). In the analyses used, we specified the robust Huber/White/sandwich estimator of variance. This estimator produces consistent standard errors even if within-group correlations are not hypothesized by the specified correlation structure (43). All analyses used an identity link so coefficients could be expressed in an easily understandable form. However, we first conducted GEE analyses using a log link in order to be sure the identity link adequately represented the data. The significance level of all analyses was set at 0.05, and all tests were 2-tailed. Statistical computations were performed using Stata, version 7.0 (43).

Biologic therapy was defined as treatment with infliximab, etanercept, or anakinra. Total costs as a function of the percent of patients receiving biologic therapy were estimated using 2001 data.

We performed various sensitivity analyses using Monte Carlo simulations with 1,000 repetitions. We simulated total costs, assuming that use of biologic therapy occurs in 0% to 100% of patients in 10% steps, and costs of drug therapy increase or decrease in 10% steps. Monte Carlo modeling was performed using Stata (43) and Tomz et al's Clarify programs (44).

RESULTS

Baseline clinical and demographic characteristics. Table 1 presents the demographic and disease status variables for the 7,527 study patients at their last questionnaire assessment. The mean age of the patients was 62 years, and the median duration of RA was 11.9 years. The median income was $35,000. Twenty-three percent of the patients were male, 8% were from minority ethnic groups, and 10% had not graduated from high school.

Among disease-related variables, 3 measures of quality of life (QOL) were available. The mean utility as measured by the SF-6D was 0.63, a number very similar to the value of 69.0 obtained with the VAS for QOL (0–100 scale). On the EuroQol, mapped from the HAQ, anxiety and depression scales, the mean utility was 0.64. The average HAQ score was 1.05, the RADAI score was 3.34, and the PCS from the SF-36 was 32.4.

Components of RA costs. Three primary components of costs (drugs, hospitalization, and outpatient procedures) and their subcomponents are summarized in Table 2. The mean total direct medical cost in 2001 was $9,519. Drug expenses represented 66% of total costs. Hospital costs and outpatient and procedure costs amounted to 17% and 16% of total costs, respectively.

The largest component of total costs was drug costs as indicated above, and these were largely determined by the cost of biologic therapy. In the study cohort the total annual direct cost for patients receiving biologic

Table 3. Univariate effect of demographic and clinical variables on total semiannual direct medical costs in RA: age- and sex-adjusted analysis*

Variable	Beta coefficient	Z score	*P*	95% CI	4th vs. 1st quartile
Clinical variables					
SF-36 PCS (0–100)	−901	−26	<0.001	−98, −84	2,351
HAQ (0–3)	1,447	25	<0.001	1,335, 1,559	2,511
SF-6D utility (0–10)†	−66	−20	<0.001	−72, −59	1,343
RADAI (0–10)	328	19	<0.001	2,934, 361	1,585
Fatigue (0–10)	204	18	<0.001	184, 227	1,489
How often depend on others (0–4)‡	1,031	17	<0.001	9,134, 1,148	
Comorbidity (0–11)	427	17	<0.001	379, 476	1,849
VAS QOL scale (0–100)	−25	−16	<0.001	28, 22	1,404
Days unable to perform usual activities (0–30)‡	130	16	<0.001	114, 146	
Depression (0–10)	312	14	<0.001	268, 357	1,262
No. of people depended on (0–7)	372	10	<0.001	295, 448	805
Work limitations (0–100)	23	7	<0.001	16, 30	1,204
Days lost from work (0–180)‡	5	6	<0.001	3, 7	
Demographic variables					
RA duration (0–10 years)	71	8	<0.001	54, 88	
RA duration (>10 years)	18	6	<0.001	12, 25	
Age (>65 years)	−40	−6	<0.001	−52, −26	
Age (0–65 years)	18	4	<0.001	9, 27	
Majority ethnic group	257	2	0.075	−26, 541	
Total income	−24	−2	0.058	−49, 1	
Education (years)	−15	−1	0.381	−47, 18	

* Beta coefficients represent the difference in costs for a 1-unit difference in the predictor variable. Clinical variables are lagged and therefore represent costs that occur in the 6 months following the clinical assessment. 95% CI = 95% confidence interval; PCS = physical component score (see Table 1 for other definitions).
† Multiplied by 10 to increase scale, since a 1-unit difference in a 0–1 variable is not useful.
‡ Difference in 4th versus 1st quartile not calculated for categorical variables treated as continuous variables in these analyses or for those with markedly skewed distributions (days lost from work and days unable to perform usual activities).

agents was $19,016, and the cost for those not receiving biologic agents was $6,164 (adjusted for age, sex, and calendar half-year); 24.7% of the patients had received biologic therapy at some time while they were enrolled in the data bank, and 26.1% were receiving biologic agents during the last 6 months of 2001.

Predictors of direct medical costs. Table 3 presents predictors of total costs among clinical and demographic variables ranked by Z score. In these analyses the clinical predictors were measured first, and the costs were those accrued over the following 6-month period. The importance of a predictor can be judged best by 2 variables in this table. The Z score is related to the *P* value and is a measure of the probability that the relationship between cost and the predictor variable occurred by chance. Because most variables in this table were statistically significant at the <0.001 level, the Z score, and not the *P* value, is better able to describe the cost–predictor relationship. Thus, the greater the absolute Z score, the more reliable or accurate is the measure. The first-versus-fourth–quartile difference measures how well the variable can predict the breadth of cost differences. The larger the first-versus-fourth–quartile difference, the more useful the variable is clinically. The first-versus-fourth–quartile difference is a method that standardizes the effect of predictor variables independent of units, and allows direct comparison among continuous predictors.

The data in Table 3 indicate that the HAQ and SF-36 PCS were the most important predictors of cost, as determined using the Z score and first-versus-fourth–quartile difference. The difference between these variables as predictors was not statistically significant, although the first-versus-fourth–quartile cost difference was greater for the HAQ. The HAQ predicted a wide range of future costs. The usefulness of the HAQ as a predictor of costs is illustrated in Figure 1. Of interest, the RADAI and the SF-6D were also useful predictors of costs, ranking just below the HAQ and PCS. However, because of the compressed scale of the SF-6D, it identified the breadth of costs slightly less effectively than the RADAI. In addition, comorbidity identified the breadth of costs well, ahead of the SF-6D and RADAI. In general, demographic variables provided less information about costs than clinical variables, and education was not a significant variable in these univariable analyses.

In addition to the relative predictive power of the variables, examination of the key variables in their original units provides important quantitative information. A 1-unit difference (higher or lower) in the HAQ

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