

# 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.

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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

RA and noted that hospitalization costs were generally  $\geq 60\%$  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 and 1998. 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](http://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

**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.

50% discount for the Yelin and Wanke study (12), so relatively comparable estimates would be available.

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
<b>Clinical variables</b>					
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	
<b>Demographic variables</b>					
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).

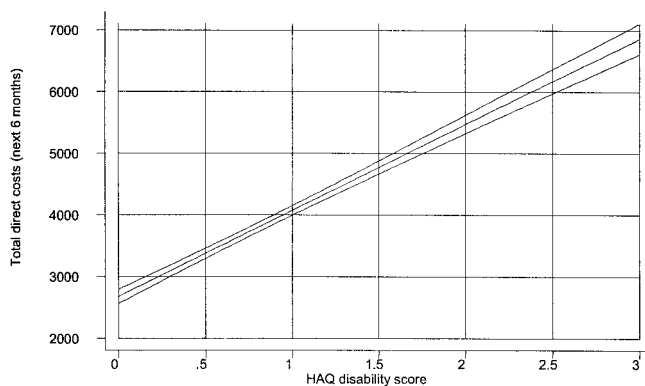
agents was \$19,016, and the cost for those not receiving biologic agents was \$6,164 (adjusted for age, sex, and calendar half-year); 24.7% of the patients had received biologic therapy at some time while they were enrolled in the data bank, and 26.1% were receiving biologic agents during the last 6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



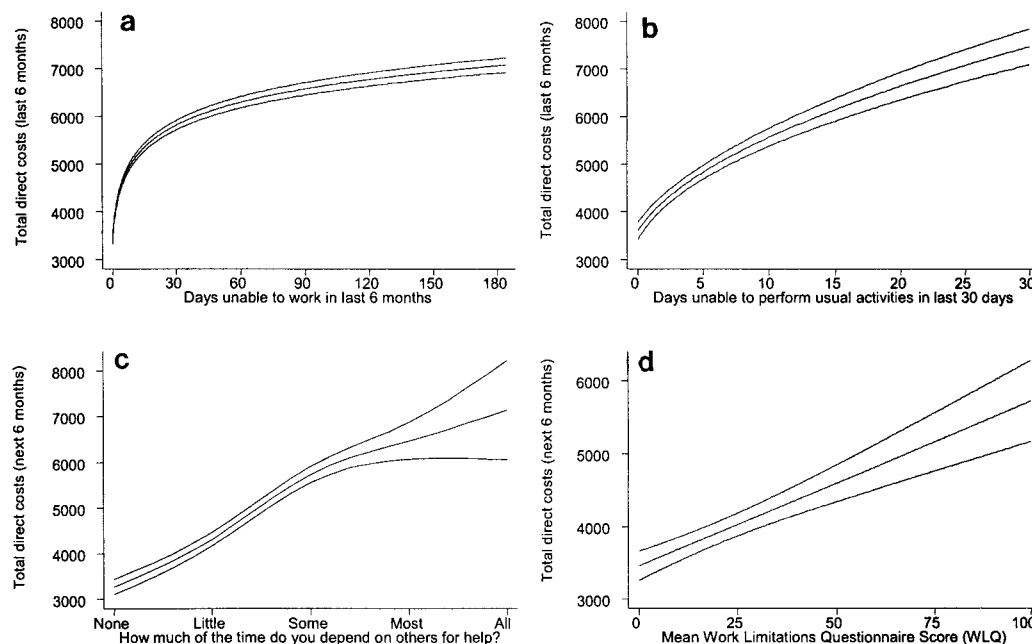
**Figure 1.** Predictive effect of the Health Assessment Questionnaire (HAQ) disability index on total direct medical costs in the 6 months following HAQ measurement, adjusted for age, sex, and calendar half-year. Lines represent predicted values and 95% confidence intervals.

score was associated with a cost difference of \$1,447 in the next 6 months. Similar values for the PCS and RADA1 were \$901 and \$328, respectively. A 10% difference in the quality of life as measured by the SF-6D resulted in a cost difference of \$656.

A series of variables related to work limitations

and dependence on others provides insight into such limitations and costs. As shown in Figure 2, persons losing time from work (Figure 2a) or from their usual activities (Figure 2b) had direct medical costs that were proportionate to the time lost. A similar finding related to work activities came from the Work Limitations Questionnaire (35,36). This questionnaire assesses difficulties at work for employed persons. As seen in Figure 2d, there was a linear relationship between costs and work limitations. Finally, persons who depend on others for help also had increased medical costs (Figure 2c). This latter, 5-choice question regarding dependence on others was simple but relatively powerful in identifying costs, as shown in Table 3. Days lost from work, days unable to work, and the Work Limitations Questionnaire were less useful and important as predictor variables (Table 3), while still demonstrating a relationship between limitations and future costs.

Because health insurance or the lack thereof is thought to influence costs, we also examined different types of insurance. Table 4 presents information on total direct medical costs by insurance type. Unadjusted costs and costs adjusted for demographic and clinical severity variables had the same ranking. In adjusted analyses,



**Figure 2.** Relationship between direct medical costs for patients with rheumatoid arthritis and limitations in activities, as assessed by **a**, number of days unable to work in the last 6 months, **b**, number of days unable to perform usual activities in the last 30 days, **c**, amount of time the patient depends on others, and **d**, total score on the Work Limitations Questionnaire. Lines represent predicted values and 95% confidence intervals.

**Table 4.** Effect of medical insurance type on total semiannual direct medical costs in RA, ranked by decreasing costs\*

Insurance type	% of patients	Costs, \$, mean (95% CI)	
		Age- and sex-adjusted analysis†	Multivariable-adjusted analysis‡
Medicaid	5.3	5,500 (5,178, 5,823)	5,133 (4,765, 5,501)
Medicare disability	2.7	5,372 (5,036, 5,708)	4,958 (4,578, 5,338)
Medicare	38.3	5,103 (4,950, 5,256)	4,798 (4,638, 4,957)
Medicare HMO	5.1	4,735 (4,497, 4,973)	4,623 (4,352, 4,893)
Private	27.8	4,461 (4,311, 4,612)	4,379 (4,214, 4,545)
PPO	7.3	4,412 (4,218, 4,607)	4,323 (4,113, 4,532)
HMO	11.6	4,172 (3,992, 4,352)	4,126 (3,931, 4,322)
No insurance	1.9	3,519 (3,186, 3,851)	2,984 (2,598, 3,371)

\* 95% CI = 95% confidence interval; HMO = health maintenance organization; PPO = preferred provider organization (see Table 1 for other definitions).

† Also adjusted for calendar half-year.

‡ Adjusted for age, sex, HAQ, RADAI, depression, fatigue, ethnic origin, income, education, RA duration, comorbidity, and calendar half-year.

patients with no insurance had low direct medical costs per 6 months (mean \$2,984). The next lowest costs were for HMO members (\$4,126). However, confidence limits overlapped between HMO, preferred provider organization (PPO), and private insurance patients. Costs were greatest for patients covered by Medicaid (\$5,133), Medicare disability (\$4,958), and Medicare (\$4,798). Costs for persons on Medicaid, Medicare, and Medicare disability were, respectively, 1.7, 1.7, and 1.6 times greater than those for persons without insurance.

Medical insurance, however, exerts its strongest effect on drug costs in circumstances where insurance coverage is incomplete or absent. As noted in Table 5, insurance coverage for medication costs varied with insurance type. The highest rate of out-of-pocket drug costs occurred in the Medicare group and in those without insurance; 77% of those without insurance paid

>25% of their drug costs, as did 47% of patients receiving Medicare. As a percentage, the least out-of-pocket costs occurred for those with private, PPO, or HMO insurance.

Actual drug costs, however, did not parallel the extremes in out-of-pocket costs noted above. Drug costs per 6 months were lowest among those without insurance (\$2,104), followed by the 2 HMO groups (\$2,344 and \$2,377). Costs were highest among Medicaid patients (\$2,711) and intermediate (~\$2,400–2,500) in the other groups. The clearest effect of insurance type was demonstrated in the percent of patients receiving biologic therapy. After adjustment for disease severity and demographic characteristics, the no-insurance group had the lowest usage of anti-tumor necrosis factor (anti-TNF) therapy (10.5%), followed by the 2 HMO groups (19.6% and 19.9%). The greatest usage was found

**Table 5.** Association between medical insurance type and semiannual drug costs in RA\*

Insurance type	% of patients paying $\geq$ 25% of drug costs	Cost, \$, mean (95% CI) (multivariable adjusted analysis)†	Receiving biologic therapy, % (95% CI)
Medicaid	17.4	2,711 (2,553, 2,870)	27.1 (21.9, 33.0)
Medicare disability	42.1	2,549 (2,374, 2,724)	31.4 (24.5, 39.2)
Medicare	47.1	2,527 (2,448, 2,606)	23.6 (21.7, 25.7)
Medicare HMO	41.4	2,377 (2,264, 2,491)	19.6 (15.4, 24.6)
Private	19.1	2,439 (2,358, 2,519)	28.0 (25.5, 30.7)
PPO	15.7	2,509 (2,386, 2,633)	27.6 (23.7, 31.9)
HMO	12.6	2,344 (2,241, 2,447)	19.9 (16.3, 24.0)
No insurance	77.1	2,104 (1,903, 2,306)	10.5 (5.5, 19.0)

\* 95% CI = 95% confidence interval; HMO = health maintenance organization; PPO = preferred provider organization (see Table 1 for other definitions).

† Adjusted for age, sex, HAQ, RADAI, depression, fatigue, ethnic origin, income, education, RA duration, comorbidity, and calendar half-year.

**Table 6.** Multivariable analysis of the effect of demographic and clinical variables on total semiannual direct medical costs in RA\*

Variable	Beta coefficient	Z score	P	95% CI
HAQ (0–3)	1,041	14	0.000	894, 1,189
RADAI (0–10)	62	3	0.008	16, 107
Depression (0–10)	74	3	0.003	24, 124
Fatigue (0–10)	42	3	0.003	14, 69
Comorbidity (0–11)	272	11	0.000	222, 322
Medical insurance				
Private	Referent			
HMO	–253	–2	0.015	–455, –50
Medicare disability	577	3	0.005	170, 984
Medicare HMO	249	2	0.105	–52, 550
Medicare	416	4	0.000	198, 634
PPO	–55	–1	0.595	–258, 148
Medicaid	748	4	0.000	348, 1,148
No insurance	–1,404	–7	0.000	–1,800, –1,008
Age (0–65 years)	–5	–1	0.410	–15, 6
Age (>65 years)	–72	–9	0.000	–89, –56
RA duration (0–10 years)	47	4	0.000	23, 71
RA duration (>10 years)	–2	–1	0.587	–10, 6
Majority ethnic group	514	3	0.001	215, 814
Education (years)	68	4	0.000	31, 104
Sex (male = 1)	156	2	0.115	–38, 349
Total income (× \$10,000)	66	4	0.000	35, 96
Calendar half-year	205	12	0.000	171, 240
Intercept (constant)	–8,105	–10	0.000	–9,694, –6,517

\* Beta coefficients represent the expected 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; HMO = health maintenance organization; PPO = preferred provider organization (see Table 1 for other definitions).

among those with Medicare disability, private insurance, and PPO insurance (31.4%, 28.0%, and 27.6%). These data suggest that insurance type is correlated with overall drug costs and with use of biologic agents.

**Disease and demographic model of total medical costs.** Table 6 presents a multivariable regression model of RA costs that include the major components of illness. Such a model allows one to understand the costs related to one variable while holding all of the other variable costs constant. The analysis partitions costs according to clinical and sociodemographic predictor variables. For clinical costs there are 4 variables that represent the major components of clinical RA: the HAQ, RADAI, depression, and fatigue scores. The HAQ represents functional status. The RADAI, which contains measures of pain, joint count, stiffness, and global severity, represents inflammation. The depression and fatigue scales represent their respective constructs. A non-RA clinical variable included in this model is comorbidity. Sociodemographic factors are represented by income, education, ethnic origin, sex, and age. Insurance status is a measure of the ability to obtain certain medical services, and calendar half-year is a measure of

inflation and provides a control for date-sensitive cost changes in drugs.

Judging predictive strength by the Z score and P value, the HAQ was the strongest predictor among clinical variables. As shown in Table 6, a 1-unit difference in the HAQ was equivalent to \$1,041 per 6 months in the multivariable model. The next strongest predictor among clinical variables was comorbidity, with a 1-unit difference in the 0–11 comorbidity scale representing a \$272 difference in costs. The RADAI, depression, and fatigue scores were weaker predictors among the clinical variables. Thus, HAQ score and comorbidity dominated clinical predictors of total direct medical costs.

Among the sociodemographic variables, costs decreased with age in persons over 65 years of age, at a rate of \$72 per year. Duration of RA increased costs during the first 10 years, at a rate of \$47 per year. Non-Hispanic whites had costs that were \$514 greater than those accrued by minority patients, and the costs were \$156 greater for men than for women. Persons with higher income and more education also had greater costs. With regard to insurance status, costs for patients in HMOs were \$253 less and the costs for those without

**Table 7.** Multivariable analysis of the effect of demographic and clinical variables on semiannual drug, hospital, and procedure costs in RA\*

Variable	Drug costs			Hospital costs			Procedure costs†		
	Beta coefficient	Z score	P	Beta coefficient	Z score	P	Beta coefficient	Z score	P
HAQ (0–3)	434	10	0.000	325	7	0.000	112	8	0.000
RADAI (0–10)	17	1	0.183	11	1	0.460	37	8	0.000
Depression (0–10)	19	1	0.185	31	2	0.052	36	6	0.000
Fatigue (0–10)	14	2	0.078	5	1	0.567	8	3	0.005
Comorbidity (0–11)	98	6	0.000	108	7	0.000	77	15	0.000
Medical insurance									
Private	Referent								
HMO	–129	–2	0.038	–58	–1	0.270	35	2	0.063
Medicare disability	121	1	0.288	231	2	0.080	157	3	0.001
Medicare HMO	–13	0	0.870	154	2	0.119	75	2	0.016
Medicare	85	1	0.179	212	3	0.002	103	5	0.000
PPO	–41	–1	0.530	–28	–1	0.641	–4	0	0.847
Medicaid	293	3	0.008	260	2	0.040	160	4	0.000
No insurance	–590	–4	0.000	–328	–3	0.001	–235	–5	0.000
Age (0–65 years)	–9	–2	0.037	3	1	0.210	3	3	0.008
Age (>65 years)	–64	–12	0.000	–2	0	0.729	–4	–2	0.016
RA duration (0–10 years)	24	4	0.000	5	1	0.526	3	1	0.240
RA duration (>10 years)	–3	–1	0.149	3	1	0.232	0	0	0.796
Majority ethnic group	443	4	0.000	67	1	0.393	–28	–1	0.456
Education (years)	57	4	0.000	–4	0	0.714	16	5	0.000
Sex (male = 1)	–125	–2	0.075	270	5	0.000	–30	–2	0.087
Total income (× \$10,000)	33	4	0.000	4	1	0.630	6	2	0.021
Calendar half-year	187	19	0.000	–6	0	0.659	7	2	0.038
Intercept (constant)	–6,471	–13	0.000	–178	–0	0.748	–514	–3	0.001

\* Beta coefficients represent the expected 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. HMO = health maintenance organization; PPO = preferred provider organization (see Table 1 for other definitions).

† Include all outpatient procedures, laboratory tests, and physician visits.

insurance were \$1,404 less when compared with private-insurance patients. In contrast, costs for those covered by Medicare and by Medicare disability, respectively, were \$416 greater and \$577 greater. The increase in costs not accounted for by clinical and demographic variables in this model was \$205 per 6 months, or \$1,230 over the 3-year study period.

**Multivariable model of cost components.** As can be seen in the calendar half-year costs presented in Table 7, almost all of the time-related costs (calendar half-year) came from increases in drug costs. Drug costs were related only to HAQ score and comorbidity among clinical variables. Aside from these differences, drug cost predictors were similar to total cost predictors, as might be expected since drug costs account for two-thirds of the total costs.

Hospital costs had a far different pattern. Time-related costs (calendar half-year) did not change significantly. Aside from the insurance variables, only male sex, HAQ score, and comorbidity predicted hospital costs.

A strikingly different pattern was seen for outpa-

tient and procedure costs. Here the RADAI, the measure of inflammation, was as good a predictor as the HAQ, and depression also played a major role. Fatigue played a significant but lesser role. In addition, for the first time in these analyses, comorbidity was a stronger predictor than the HAQ. Most sociodemographic variables were significant in this analysis.

**Sensitivity analyses.** Costs in RA change predominantly as a result of drug therapy (Table 7), particularly biologic therapy. It is to be expected that the number of patients receiving biologic agents may change, as might the cost of that therapy. Table 8 and Figure 3 present data based on Monte Carlo simulations from the data of the current study that vary the percent of patients receiving biologic therapy and the cost of that therapy. For ease of using these data, Table 8 and Figure 3 present annual costs. For example, if the prevalence of biologic therapy in RA patients were to rise to 40% and the cost of the therapy to increase by 20%, the expected total direct medical cost per year would be \$12,616, compared with the \$9,519 reported here. As another example, if regulation and competition were to restrain

**Table 8.** Total annual direct medical costs (\$) as a function of the percent of RA patients receiving biologic agents and future increase or decrease in the cost of biologic agents\*

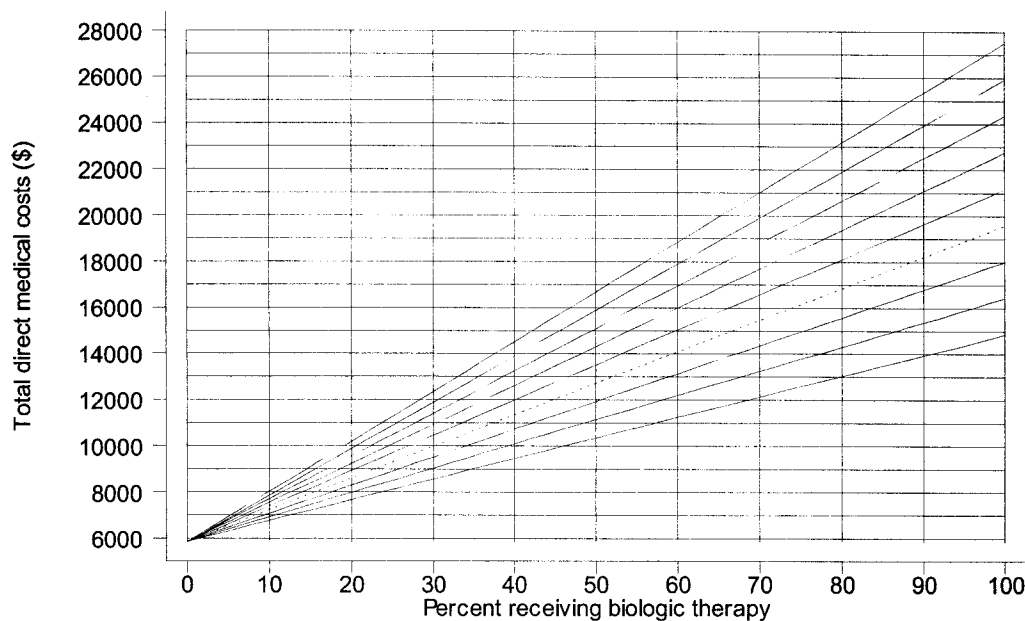
% use	Decreasing costs			Current	Increasing costs				
	-30%	-20%	-10%		+10%	+20%	+30%	+40%	+50%
0	5,866	5,866	5,864	5,862	5,858	5,856	5,854	5,852	5,852
10	6,762	6,920	7,078	7,234	7,390	7,546	7,704	7,858	8,018
20	7,660	7,976	8,292	8,608	8,922	9,236	9,552	9,866	10,184
30	8,556	9,032	9,506	9,980	10,452	10,926	11,402	11,874	12,350
40	9,454	10,086	10,720	11,352	11,984	12,616	13,250	13,882	14,516
50	10,350	11,142	11,934	12,726	13,516	14,306	15,100	15,890	16,682
60	11,246	12,198	13,148	14,098	15,046	15,996	16,948	17,896	18,848
70	12,144	13,254	14,362	15,470	16,578	17,688	18,798	19,904	21,014
80	13,040	14,308	15,576	16,844	18,110	19,378	20,646	21,912	23,180
90	13,938	15,364	16,790	18,216	19,642	21,068	22,496	23,920	25,346
100	14,834	16,420	18,004	19,588	21,172	22,758	24,344	25,926	27,512

\* The “baseline” case in the current analysis is at 25% of use (between 20% and 30%) in the Current column.

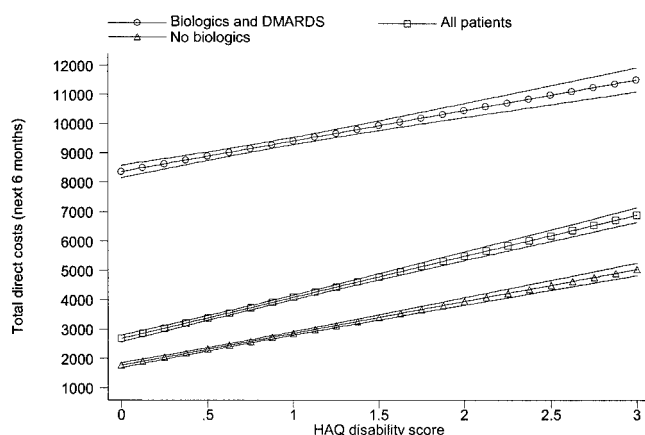
usage at 30% but decrease cost by 20%, the expected total direct medical cost would be \$9,032 per year. Data on 95% confidence intervals for the values in Table 8 are available from the authors. Figure 4 shows the relationship between costs and HAQ score as a function of biologic therapy; it appears reasonable to extrapolate from these curves to the relationship between HAQ score and costs in general.

### DISCUSSION

The results of this study indicate that the mean direct medical care costs in RA are at least \$9,519 per year. Of the total costs, drug costs account for 66% and hospital costs for 17%. The drug costs are driven predominantly by biologic therapy. Approximately 25% of patients received biologic therapy, and the direct annual



**Figure 3.** Nomogram of total annual direct medical costs in relation to prevalence of use of biologic therapy, based on Monte Carlo simulation studies. Dotted line represents costs based on current costs in this study. Lines above the dotted line represent costs if the costs of biologic therapy increased by 10%, 20%, 30%, 40%, or 50%; lines below the dotted line represent costs if the costs decreased by 10%, 20%, or 30%..



**Figure 4.** Increase in total direct medical costs as a function of Health Assessment Questionnaire (HAQ) disability score, in all patients regardless of biologic or disease-modifying antirheumatic drug (DMARD) therapy (All patients), patients receiving biologic therapy regardless of DMARD use (Biologics and DMARDs), and patients not receiving biologic therapy (No biologics). The No biologics category includes both DMARD-treated and non-DMARD-treated patients. Lines represent predicted values and 95% confidence intervals.

medical care cost for those receiving biologic agents was \$12,852 greater than that for those not receiving these agents. Patients with RA with poor function incur substantially higher drug and hospitalization costs. Increased education, income, and majority ethnic status were all associated with increased drug costs but not with hospitalization costs.

As expected, our direct medical care cost estimates in RA are substantially higher than cost estimates before the biologic therapy era (1–14). As noted above, the low end of annual direct medical costs before the biologic therapy era ranged between \$2,162 and \$3,802 (\$3,802 as charges rather than costs) (9,11,13), with an overall average annual direct cost of \$5,425 reported in Pugner et al's 2000 review of previous cost studies (2–10,15). The previous estimate closest to ours was that of Yelin and Wanke (12). They reported the annual total direct medical care costs for their 272 northern California RA patients to be \$8,501 in 1995–1996. Discounting their hospital costs by 50% as they recommended (\$5,876), subtracting their costs due to travel, paid help, and medical devices that we did not measure in our study (\$5,682), and taking into account inflation, their total annual cost would be \$6,414. This is similar to our result of \$5,850 from a Monte Carlo simulation using their study's characteristics (average age, sex, ethnicity, disease duration, pain scale, HAQ, comorbidities, and *no biologic agents*).

Nevertheless, the 50% reduction in hospital costs suggested by Yelin and Wanke still does not make the Medicare costs used in our study equivalent to their hospitalization costs. In addition, the mean duration of disease among participants in their study at its conclusion was 17.9 years, as opposed to 15.0 years in the current report. The risk of total joint replacement has been shown to increase with time at a rate of ~1.1% per year of RA (45). The net results of the simulation studies and these additional differences suggest strongly that the actual findings of Yelin and Wanke's study and our study are essentially equivalent, except for the addition of biologic therapy.

Medical care costs appear to be primarily driven by drug costs in the biologic therapy era. Before the biologic therapy era, studies showed hospitalization costs to generally account for  $\geq 60\%$  of direct medical costs, and drug costs for  $\leq 20\%$ . In contrast, our results show the reverse of these proportions between the two costs. While this change is primarily due to the high cost of biologic agents, it remains possible that hospitalization costs may be reduced by more effective treatments with biologic agents.

A number of factors could influence drug costs in the future. The most probable determinant of future drug costs is an increase in the proportion of patients receiving biologic therapies, driven in part by the acceptability of the drugs and the expected introduction of new biologic agents in 2003 and after. However, there might be factors working to decrease these current costs. It is possible that the introduction of competing biologic agents might lead to a reduction in charges for these drugs. Additionally, accumulating experience with biologic agents is likely to lead to insurance companies' requiring more sharing of costs by patients, with the result that fewer patients may be able to afford the medications. A further consideration is that severity screening might lead to a reduction in the number of patients eligible to receive biologic therapy.

To account for these possibilities, we have performed Monte Carlo simulation studies using the data in this report. With the data from Table 8 and Figure 3, it is possible to predict costs based on the increase or decrease in drug costs as well as the prevalence of biologic therapy use in the community. One example for doing this that might be germane to the current report involves dosing with infliximab. As noted in Patients and Methods, if the dose of infliximab were increased in clinical practice to 5 mg/kg rather than the ~4 mg/kg caused by rounding to the nearest 100 mg (using the remainder of the vial), there would be an increase in

infliximab costs of 25% and an overall increase in costs of 10.9%. If this were done in half of the infliximab-treated patients, costs would increase by ~5.5%. From Table 8 and Figure 3, a 5.5% increase in drug costs can be extrapolated easily to obtain a new estimate of total medical costs. When new estimates of total costs are obtained, the standardized cost coefficients (Table 3) can be applied to obtain updated estimates of variable contributions to costs.

The key clinical factors in predicting future costs are functional disability and comorbidity. In fact, these variables dominate the individual sociodemographic variables. It does not matter whether the HAQ or the SF-36 PCS is used to measure functional status since both function equally well; however, no other clinical or demographic variables approach their predictive strength. A 1-unit difference in the HAQ score predicts a \$1,447 difference in total costs over the next 6 months (Table 3), and in a multivariable model it predicts a \$1,041 difference (Table 6). A 1-unit difference in these 2 variables combined predicts \$1,313 (95% confidence interval \$1,163, \$1,463) in future costs. Comorbidity is not difficult to measure by questionnaire, and HAQ measurement is simple. Therefore, these 2 tools can provide a rapid and reliable measure of future costs. The RADAI (25), an instrument that is as effective as American College of Rheumatology improvement criteria (46) in clinical trials, does not predict total costs well. This is an indication that function, rather than clinical activity, is the key factor in RA costs.

Some of the factors that predict individual cost components are of interest. Hospitalization costs (Table 7) are essentially predicted by the HAQ score, comorbidity, and sex, but outpatient costs are responsive to a very different set of variables. In addition to the HAQ score, the RADAI and depression are predictors of outpatient costs (of almost equal importance), and comorbidity is an even stronger predictor than the RADAI and depression scores. Education and income are also predictors of costs for outpatient care. Drug costs (Table 5) were influenced somewhat by insurance. HMO patients and the uninsured had lower costs and were least likely to be receiving anti-TNF therapy. In contrast, Medicaid patients had higher costs. Drug costs also increased with RA duration during the first 10 years of illness, and drug costs for non-Hispanic white patients were \$443 greater per 6 months than for minority patients.

We believe our results break new ground in several ways. First, the study measures costs in a representative sample in an era of biologic therapy where the

major determinant of cost is the biologic therapy itself. Such data have not been available previously. Second, it provides a wide variety of predictor variables in the area of clinical and sociodemographic factors. Third, it provides detailed cost measurements from a very large contemporary sample of 7,527 RA patients and 25,050 observations in a 3-year period.

There are a number of potential limitations to this study. We obtained costs for drugs from the Federal Upper Limit or wholesale rates according to *Drug Topics Red Book*, and actual costs in practice may be higher. This is also the case for nondrug costs, for which we used Medicare rates. We used these rates so standard, comparable, and nationally recognized methods could be applied. At the time of the preparation of the manuscript we were unable to obtain information on infliximab dose by patient self-report, and it is possible we may have underestimated usage. However, if more accurate data become available, Table 8 and Figure 3 can be used to provide updated cost estimates. Participants in longitudinal studies may differ systematically from nonparticipants in terms of social, demographic, and disease severity characteristics. Disease is slightly more severe in nonparticipants, but nonparticipants may have less access to insurance or may have other reasons to use fewer drugs. The effect of nonparticipation cannot be fully described, but it is likely to be small. In addition, because of the national nature of our study and use of specialty and nonspecialty physicians by the patients, we were unable to measure travel costs. Finally, the data from this study should be used with caution in predicting cost changes associated with particular treatments, since we did not specifically evaluate treatment-related cost changes.

In summary, current direct medical cost estimates in RA are substantially higher than cost estimates before the biologic therapy era, and costs are now driven predominantly by drug costs, primarily for 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 determining costs.

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