Longer Use of COX-2-Specific Inhibitors Compared to Nonspecific Nonsteroidal Antiinflammatory Drugs: A Longitudinal Study of 3639 Patients in Community Practice

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ABSTRACT. ***Objective.*** To compare COX-2-specific inhibitor therapy with conventional nonspecific nonsteroidal antiinflammatory drugs (NS NSAID), and investigate the effect of demographic and disease factors on NSAID duration of use.

Methods. A total of 3639 patients with rheumatoid arthritis (RA), osteoarthritis, and fibromyalgia starting therapy of celecoxib, rofecoxib, naproxen, or ibuprofen were surveyed at 6-month intervals for up to 2.5 years. Detailed demographic and disease severity variables were also measured. Time to discontinuation, discontinuation rates, and effect of covariates were determined by Weibull parametric survival analyses, controlling for a wide variety of demographic and disease severity factors.

Results. The median duration of use for celecoxib, rofecoxib, naproxen, and ibuprofen was 15, 13, 10, and 10 months, respectively. Duration of use of celecoxib and rofecoxib, as measured by survival times, was significantly longer than those of naproxen and ibuprofen. The celecoxib survival time was significantly longer than the rofecoxib survival time ($p = 0.005$). Disease severity was not associated with survival times, but survival was related to younger age and male sex. In addition, ulcer diagnosis was a strong predictor of early termination. After adjustment for severity, survival times for RA and non-RA patients were the same.

Conclusion. COX-2-specific inhibitors have a longer duration of use than NS NSAID. Among the COX-2-specific inhibitors, celecoxib has a longer survival time than rofecoxib. In addition, COX-2-specific inhibitors also have longer survival times than noted in the literature of NS NSAID in RA community practice. Duration of use can be an indicator of treatment effectiveness and/or drug acceptability, and provides additional interpretation beyond the results of clinical trials. (J Rheumatol 2004;31:355–8)

Key Indexing Terms:

NONSTEROIDAL ANTIINFLAMMATORY DRUGS | COX-2-SPECIFIC INHIBITORS | DISCONTINUATION | SURVIVAL ANALYSIS | CELECOXIB | ROFECOXIB | NAPROXEN | IBUPROFEN

Patients with rheumatoid disorders frequently change treatments. Nowhere is this more common than with nonsteroidal antiinflammatory drugs (NSAID)[1-3]. Given the chronic nature of rheumatic disorders, treatment discontinuation can imply insufficient efficacy, unacceptable toxicity, or both. Yet measurement of time to discontinuation may provide a comparative measure of NSAID effectiveness and treatment acceptability.

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Although results from randomized clinical trials suggest general equivalence among NSAID, experience in practice may be different. We have recently shown that confounding by indication and channeling bias resulted in adverse selection for celecoxib immediately after its release[4], and similar processes work in the perception of physicians regarding other new agents such as rofecoxib and meloxicam.

In addition to the innate efficacy and toxicity of NSAID, a number of demographic factors might influence drug acceptability, including age, sex, education, income, and comorbid status. In addition, disease severity factors related to pain, function, fatigue, and steroid use might contribute, as might ulcer symptoms and ulcer diagnosis. These factors have not been studied as predictors in the community setting, but might be important in understanding treatment termination.

In this study we had 3 main objectives: (1) to understand contemporary survival time using modern drugs, including COX-2-specific inhibitors; (2) to understand the overall acceptability of COX-2-specific inhibitors compared to

nonspecific NSAID (NS NSAID); and (3) to understand features of rheumatic disease illness and its treatment, including channeling effects, that might contribute to increased or decreased NSAID survival time. To this background we bring data from a large, prospective, longitudinal study to illuminate these issues.

MATERIALS AND METHODS

Patient population. This study was performed using patients who were participants in 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[4-6]. Patients in this study had either a diagnosis of rheumatoid arthritis (RA), osteoarthritis (OA) of the hip or knee, or fibromyalgia. All diagnoses were made by the patients' rheumatologists.

Beginning with the survey of July 1999, we identified patients with rheumatic disease who completed detailed postal surveys at 6-month intervals during a followup period of up to 2.5 years. To analyze duration of NSAID therapy and factors associated with it, we restricted analyses to the 4 most commonly used NSAID (11,484 patients) and then, further, to patients starting one of those NSAID for the first time during the NDB period of observation. Each patient contributed one NSAID treatment course to the analysis. In the case where patients received more than one NSAID during the study period, a random number generator was used to identify the drug to be included in the analyses.

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, and total family income. Disease status and activity variables included the Stanford Health Assessment Questionnaire functional disability index (HAQ disability)[7,8] and a visual analog scale (VAS) for pain and fatigue[9]. Patients also reported general medical symptoms, which were then converted to a count of somatic symptoms[4,10]. The symptom scale ranged from 0 to 38. The comorbidity score represented the sum of 11 comorbid conditions, as reported[11]. In addition, patients reported whether they had been diagnosed by a physician within the previous 6 months as having a gastrointestinal (GI) ulcer. Patients also reported all drugs and dates of starting and stopping drugs for the previous 6 months. For the purposes of this study, drug discontinuation occurred at the month of discontinuation indicated by the patient.

Baseline characteristics among the study groups (Table 1) were analyzed using one-way analysis of variance for continuous variables and chi-square analysis for categorical variables. Survival data were analyzed using Weibull regression analysis with time-varying covariates. Weibull analysis was chosen after examination of the baseline hazard showed a nonproportional, decreasing hazard over time. To control for possible differences in patient characteristics, data were adjusted for various covariates. In the simplest case, only demographic variables and nonarthritis variables were included: age, sex, education, income, ethnic origin, duration, comorbidity, and calendar month and year of drug start. A second analysis added HAQ, pain, fatigue, symptom count, and prednisone use. A third analysis added the diagnosis of GI ulcer during the preceding 6 months. Clinical variables represented baseline predictors. All tests were 2-tailed. The significance level was set at 0.05.

RESULTS

Table 1 presents the mean and percentage values of the key study variables for the study patients. Because of the large sample size, most differences among treatment groups were statistically significant although not necessarily clinically relevant. Patients receiving COX-2-specific inhibitors were, on average, about 3 years older than users of NS NSAID. More pertinent to illness severity, HAQ scores were 0.1 to 0.2 units greater and pain scores were about 0.4 to 0.5 units greater for COX-2-specific inhibitor versus NSAID users. Similarly, COX-2-specific inhibitor users had a greater comorbidity score, more somatic symptoms, and greater prednisone use. Taken as a whole, these data indicate that illness severity was greater among COX-2-specific inhibitor users.

Table 2 analyzes the risk of discontinuation according to NSAID. In these Weibull regression analyses, 3 separate models were studied. The first model (model 1) controls for demographic factors; the second (model 2) for demographic plus disease severity factors; and the third (model 3) additionally controls for a diagnosis of a GI ulcer within the last 6 months. Regardless of model, Table 2 indicates that compared to celecoxib and rofecoxib, all of the NS NSAID have higher rates of discontinuation. Celecoxib also differs from rofecoxib at p = 0.002 to p = 0.005. Differences in survival time for naproxen versus ibuprofen were not significant in any model.

The results of the final model (model 3) are shown graph-

Table 1. Mean and percentage values of study variables at first observation (n = 3639). The p values represent overall difference by one-way analysis of variance for continuous variables and by chi-square analysis for categorical variables.

Variable	Celecoxib	Rofecoxib	Naproxen	Ibuprofen	Total	p
Patients, n	1319	1249	409	662	3639	
Age, yrs	63.0	62.8	60.1	57.6	61.6	< 0.001
Sex, % male	21.0	15.2	22.0	17.4	18.5	< 0.001
HAQ (0–3)	1.1	1.2	1.0	0.9	1.1	< 0.001
Pain (0–10)	4.1	4.4	3.9	3.7	4.1	< 0.001
Fatigue (0–10)	4.5	4.8	4.3	4.3	4.5	< 0.001
RA, %	76.8	67.3	71.6	68.1	71.4	< 0.001
High school graduate, %	89.8	90.0	89.7	91.8	90.2	0.498
Ulcer diagnosis, % last 6 mos	3.4	4.2	2.2	1.8	3.3	0.021
Count of somatic symptoms (0–38)	7.4	8.4	7.1	7.1	7.7	< 0.001
Current comorbidity count	0.8	0.9	0.8	0.7	0.8	< 0.001
Total income, $1000 US	44	45	43	48	45	0.006
Majority ethnic status, %	90.9	93.0	92.2	91.2	91.8	0.230
Prednisone, %	30.3	25.8	23.5	22.2	26.5	< 0.001

Table 2. Hazard ratios for discontinuation in 3 models (n = 3639). Rofecoxib differs significantly from naproxen and ibuprofen in all 3 models.

Model Variable	Hazard Ratio	p	95% CI
1			
Celecoxib	Reference		
Rofecoxib	1.18	0.002	1.06, 1.32
Naproxen	1.53	< 0.001	1.32, 1.78
Ibuprofen	1.46	< 0.001	1.28, 1.66
2			
Celecoxib	Reference		
Rofecoxib	1.17	0.004	1.05, 1.31
Naproxen	1.55	< 0.001	1.33, 1.80
Ibuprofen	1.47	< 0.001	1.29, 1.67
3			
Celecoxib	Reference		
Rofecoxib	1.17	0.005	1.05, 1.30
Naproxen	1.54	< 0.001	1.33, 1.80
Ibuprofen	1.47	< 0.001	1.29, 1.67

Adjustment 1: adjusts for age, sex, education, income, ethnic origin, duration, comorbidity, RA, and calendar month and year of drug start. Adjustment 2: adjusts for variables in adjustment 1 plus HAQ, pain, fatigue, symptom count, and prednisone use. Adjustment 3: adjusts for variables in adjustment 2 plus the diagnosis of GI ulcer.

ically in Figure 1. This figure also indicates that 50% of patients taking celecoxib, rofecoxib, naproxen, and ibuprofen will discontinue their NSAID at 15, 13, 10, and 10 months after start, respectively. Discontinuation times for 25%, 50%, and 75% by treatment are presented in Table 3.

Table 4 shows the details of the final (model 3) regression analysis. In this multivariable analysis that controls for key illness factors, RA patients and men are less likely to discontinue NSAID, and older persons and those with high

Table 3. Time (in months) to discontinuation for study NSAID adjusted for study covariates.

Drug	n	Time at Risk	25%	50%	75%
Celecoxib	1319	12200	6	15	*
Rofecoxib	1249	10577	5	13	27
Naproxen	409	2742	4	10	20
Ibuprofen	662	4620	4	10	21

* The 75th percentile was not reached by study end.

school education are significantly more likely to have shorter survival times. Among the clinical variables, only a diagnosis of a GI ulcer by a physician has any significant association [hazard ratio 1.7, 95% confidence interval (CI) 1.3, 2.1], and HAQ, pain, and fatigue are not significant in the model.

DISCUSSION

Our results indicate that there are differences in survival time among the 4 NSAID. To the extent that these differences are a measure of NSAID acceptability, celecoxib is more acceptable than traditional NSAID and differs significantly from rofecoxib at the p = 0.005 level.

There are only a few studies of community practice. Wijnands, *et al* studied 148 patients in 1991 who were recently diagnosed with RA and were started on an NSAID[12]. At one year, 41% had discontinued indomethacin, but only 14% had stopped naproxen, and 19% had stopped diclofenac. Luggen, *et al* studied 188 NSAID starts in patients with RA in 1989[1]. Approximately 25% of patients taking naproxen and 50% of patients taking other NSAID discontinued by one year after initiation. Pincus and colleagues studied 1775 courses of NSAID in 532 patients

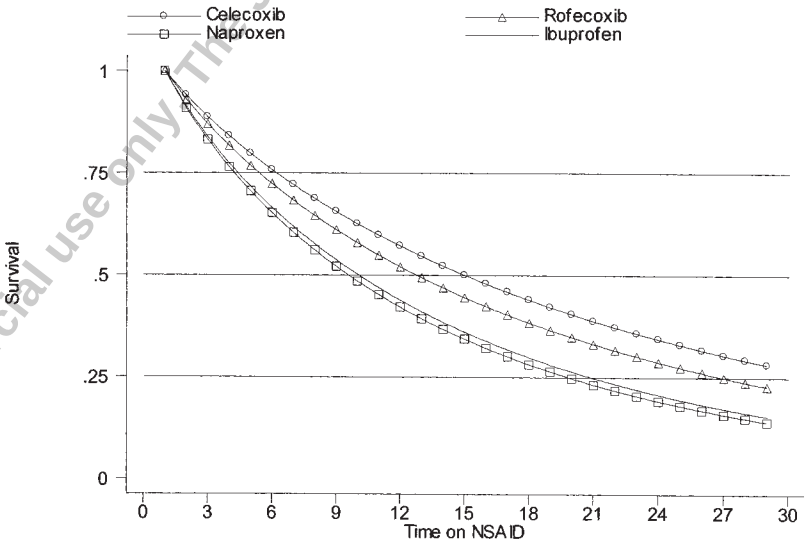

Figure 1. Survival analysis of 4 NSAID adjusted for study covariates. The 50% survival times for celecoxib, rofecoxib, naproxen, and ibuprofen were 15, 13, 10, and 10 months, respectively. Celecoxib and rofecoxib survival differed from the other NSAID at p < 0.001. Celecoxib and rofecoxib were significantly different as well (p = 0.005).

Table 4. Multivariate hazard ratios for discontinuation (n = 3639).

Variable	Hazard Ratio	p	95% CI
Celebrex	Reference		
Rofecoxib	1.17	0.005	1.05, 1.30
Naproxen	1.54	0.000	1.33, 1.80
Ibuprofen	1.47	0.000	1.29, 1.67
Pain (0–10)	1.02	0.085	1.00, 1.04
Fatigue (0–10)	1.01	0.627	0.98, 1.03
HAQ (0–1)	0.96	0.383	0.88, 1.05
Age, yrs	1.01	0.014	1.00, 1.01
Sex (male = 1)	0.79	0.000	0.70, 0.90
Month/year of NSAID start	1.00	0.877	0.94, 1.05
Ulcer diagnosis	1.65	0.000	1.33, 2.06
Current comorbidity count	1.04	0.084	0.99, 1.09
Symptom count (0–38)	1.01	0.024	1.00, 1.02
Prednisone, %	0.95	0.390	0.85, 1.06
High school graduate, %	1.34	0.000	1.14, 1.58
Majority ethnic status, %	1.04	0.688	0.87, 1.23
Income, US $1000	1.00	0.628	1.00, 1.00
Disease duration, yrs	1.00	0.055	0.99, 1.00
RA, % (RA = 1)	0.86	0.005	0.77, 0.96

with RA in the practices of 7 community rheumatologists[2]. Fifty-two percent of patients had discontinued their NSAID 12 months after starting, and 64% had discontinued within 2 years after starting. Scholes, *et al* in a retrospective cohort study of Health Maintenance Organization enrollees, studied 1405 patients with OA aged 45 or older who received a new prescription for one of 4 NSAID[3]. Only 15 to 20% of those starting the study NSAID were still using the same drug at the end of the 12 months. Our report is most similar in its methods and demographics to the report of Pincus, *et al*[2] and our results for NS NSAID mirror their report. However, the result of the COX-2-specific inhibitor drugs are better than those noted in their study.

As the study of Scholes, *et al* indicates, drug survival in patients with OA in a community setting is rather short[3]. We also confirm a difference in survival time for OA compared to RA (OR 0.86, 95% CI 0.77, 0.96), but the difference is slight (odds ratio difference = 16%). The better survival time among patients with OA in this study may be the result of a more severe level of illness than is likely to be found in a health maintenance organization sample derived from an insurance diagnosis of OA, as reported by Scholes, *et al*. Such patients would not be expected to have substantial chronic illness. In addition, the Scholes, *et al* report did not account for severity, as was the case in the current report.

The fact that we did not find disease severity variables to be predictors suggests that it is the NSAID themselves rather than disease severity that leads to discontinuation. Discontinuation was related to ulcer diagnosis, as might be expected, and to age, sex, and education level.

Among the limitations of our study is that patients participating are respondents in a survey and may differ from nonrespondents. However, we found no evidence that demographic factors such as income and ethnicity played any role in the discontinuation process, nor was disease severity a significant marker, even though respondents and nonrespondents usually differ in severity. It is possible that advertising of the COX-2-specific inhibitors might have influenced survival time in ways that we are not able to determine. Finally, observational studies may have biases that are not clearly determinable.

In summary, the 50% survival times for celecoxib, rofecoxib, naproxen, and ibuprofen were 15, 13, 10, and 10 months. The celecoxib and rofecoxib survival times differed significantly from those of naproxen and ibuprofen, and celecoxib had longer survival than rofecoxib. Disease severity factors were not associated with survival times, but longer survival was related to younger age, being male, and having RA. In addition, COX-2-specific inhibitors also have longer survival times than noted in the literature of NS NSAID in RA community practice.

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