Corticosteroid Use in Rheumatoid Arthritis: Prevalence, Predictors, Correlates, and Outcomes

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ABSTRACT. ***Objective***. To determine the rate of current and lifetime use of corticosteroids, the degree of association between corticosteroids and rheumatoid arthritis (RA) activity and outcome, corticosteroid initiation and discontinuation rates, and the predictors associated with initiation and discontinuation.

Methods. A total of 12,749 patients with RA were evaluated semiannually as to corticosteroid use, RA activity measures, RA outcomes, and predictors of initiation and discontinuation of corticosteroids.

Results. Current corticosteroid use was 35.5% and lifetime use was 65.5%. Rheumatologists varied substantially in their use of corticosteroids. The primary patient-derived determinant of corticosteroid initiation, current use, and discontinuation was symptom severity, although 21–25% of patients in remission or with minimal disease activity continued taking corticosteroids. Within the pool of current users, 24.3% [95% confidence interval (CI) 23.2–25.3%] discontinued corticosteroids yearly, and among patients newly starting corticosteroids this rate was 56.9% (95% CI 53.4–60.7%). Corticosteroid initiation occurred at a rate of 8.9% (95% CI 8.4–9.3%) per year. Among corticosteroid users, persistent use (> 5 years) occurs in about one-third of patients. Corticosteroid use and duration of use is associated with severe outcomes for current and past users. For current users versus non-current users, covariate adjusted outcomes were: mortality 5.7% versus 2.6%, work disability 28.4% versus 17.2%, and total joint replacement 18.5% versus 13.0%.

Conclusion. Corticosteroid use is dynamic and is associated with RA severity. Corticosteroid use is also associated with adverse longterm outcomes, but the ability to discern causal associations is severely limited by confounding by indication. The idea of "once on corticosteroids, always on corticosteroids" is incorrect and applies to only a minority of patients. (First Release Jan 15 2007; J Rheumatol 2007;34:696–705)

Key Indexing Terms:
TREATMENT RHEUMATOID ARTHRITIS PREDNISONE
CORTICOSTEROIDS SEVERITY DISEASE MODIFYING ANTIRHEUMATIC DRUGS

Corticosteroids have an unusual place in the treatment of rheumatoid arthritis (RA). For 60 years since their discovery, arthritis experts and generalists have disputed the effectiveness, toxicity, indications, and timing of use of these agents[1-3]. Randomized controlled trials (RCT) of low-dose corticosteroids suggest that benefits include symptomatic relief[4,5] and retardation of radiographic progression[6,7]. Reported rates of adverse events have been rare in RCT[8], but the trials have been small and too short to detect infrequent or delayed adverse outcomes. Corticosteroid use is linked to adverse effects, including osteoporosis, cataracts, infection, gastrointestinal ulceration, and cardiovascular disease[1,7,9-18]. The central question in rheumatology is whether the benefits of corticosteroids outweigh their disadvantages, particularly considering the low doses used in the treatment of RA.

Observational data that can address the risk-benefit questions are not without problems. Channeling bias, or confounding by indication, results when corticosteroids are prescribed to those patients with the worst prognosis. Although theoretically it may be possible to control statistically for such biases, statistical adjustment requires access to all the relevant covariates that influence the initiation and discontinuation of corticosteroids. In addition, meticulous followup of all covariates is required over the entire course of RA — a course that can exceed 30 years. Randomized trials, the optimal way to deal with confounding, cannot be employed for more than a fraction of the duration of RA. Unfortunately, longterm benefits and adverse outcomes thought to be linked to corticosteroids may occur late in the course of RA. Problems of con-

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founding and incomplete and short-term followup have severely limited our ability to understand the longterm risk-benefit of corticosteroids and have engendered and sustained the corticosteroid controversy.

In addition to disease activity and severity factors, physician training and beliefs may influence corticosteroid usage. Criswell and colleagues suggested that the characteristics of the prescribing rheumatologist rather than patient-specific factors better explained corticosteroid use[19,20]. However, there are virtually no data regarding rates of initiation of corticosteroids, and very sparse data on the demographic, clinical factors, and outcomes related to its administration. In one of the few articles on the subject, Kremers, *et al* reported that the percentage of patients with RA in Olmsted County, Minnesota, exposed to corticosteroids at any time during their disease course increased steadily from 1955 to 1995[21]. Ward and Fries also noted a trend towards increasing corticosteroid use among physicians from 1981 to 1996 but, like Kremers, *et al*, offered no further analysis of corticosteroid exposure[22]. Thus, patients using these drugs have not been characterized, and there are few robust data on prevalence.

The purpose of the research described below is to describe patterns and rates of use of corticosteroids, describe the levels of disease activity and outcomes of corticosteroid users, and to describe factors relating to initiation and discontinuation of corticosteroids. Although RA outcomes are severely confounded by RA severity, the association between outcomes and corticosteroid use provide benchmarks for the associations of contemporary corticosteroid use. Such data may be of use to clinicians as they attempt to sort out whether the observed outcomes are attributable only to RA severity, only to corticosteroids, or to some combination of RA and corticosteroid use.

MATERIALS AND METHODS

Study sample. Patients in our study were 21,672 participants in the National Data Bank for Rheumatic Diseases (NDB) longitudinal observational study of RA outcomes between January 1, 1999 and December 30, 2004. NDB participants are recruited on an ongoing basis from the practices of United States rheumatologists, and are followed prospectively with semiannual, detailed, 28-page questionnaires, as previously described[23-27]. In general, except for safety registries, we requested that enrollees be unselected as to severity. The average number of questionnaires completed by each patient was 5.2. Of the study patients, 8,923 entered the NDB as part of drug safety registries. Referrals to the RA data bank were made from the practices of 1,052 US rheumatologists.

For the purposes of obtaining prevalence of corticosteroid (also called prednisone in this report) use in patients who did not have RA or any other inflammatory disorder, we studied a random observation from each of 5,466 NDB participants with noninflammatory rheumatic disorders (NIRD), such as osteoarthritis, back pain syndromes, fibromyalgia, etc. We did this to determine the prevalence of corticosteroid use that cannot be attributable to RA alone. As with the RA patients, we randomly selected a single observation (6 month questionnaire) for study.

Study assessments. At each questionnaire assessment, we recorded socioeconomic and demographic variables as well as treatments. At the time of enrollment in the NDB, we determined the duration of use of specific treatments prior to enrollment. Patients also reported functional status using the Health Assessment Questionnaire (HAQ)[28,29]. We determined pain, global severity, and fatigue by visual analog scales (VAS)[30]. The VAS measure 21 points, from 0 to 10 at 0.5 unit intervals.

To assess RA activity we computed the Patient Activity Scale (PAS) by multiplying the HAQ by 3.33 and then dividing the sum of the VAS pain, VAS global, and re-scaled HAQ by 3. This yields a 0–10 scale with good psychometric properties[31]. We also used the PAS scale to classify patients who were in remission (PAS $\leq$ 0.5)[32] [and unpublished observation: F. Wolfe. Minimal disease activity (MDA), remission and the long-term outcomes of rheumatoid arthritis. 2006] or in a MDA state (PAS < 1.625) (unpublished observation: Wolfe, see above) according to the OMERACT definition[33]. An additional method to determine minimal disease/normal status, based on previously published Medical Outcomes Study Short Form 36 (SF-36) values for normal (non-RA) populations, is described in the statistical section, below.

Global measures of health included the SF-36 Physical Component Scale (PCS) and Mental Component Scale (MCS)[34,35]. The effect of comorbidity was assessed by a comorbidity score, which is the sum of 11 present or past comorbid conditions reported by the patient. Conditions include cancer, stroke, fracture, renal, neurologic, endocrine, gastrointestinal, cardiovascular, pulmonary, genitourinary, and psychiatric problems.

In addition to these data, patients reported all previous and current medication use (including dose and frequency), joint replacement surgery, and US Social Security disability awards. We defined treatment with a disease modifying antirheumatic drug (DMARD) to be treatment with any one of the following drugs: leflunomide, auranofin, azathioprine, sulfasalazine, cyclosporine, cyclophosphamide, injectable gold, minocycline, penicillamine, hydroxychloroquine, or methotrexate. Biologic drug treatment included treatment with any of the following: etanercept, infliximab, adalimumab, or anakinra. Analysis of disability awards was restricted to patients < 62 years of age, the age at which retirement pension becomes available under the US Social Security system. Data on deaths were obtained from family and physicians, and from yearly systematic searches of the National Death Index (NDI)[36,37]. Therefore, death data were available for all participants regardless of whether they discontinued participation in the study prior to death.

Cross-sectional analyses comparing current users and non-users of corticosteroids. In these analyses (Table 1 and associated text), we studied a random observation from each of 12,749 patients with RA to obtain crude prevalence estimates of oral corticosteroid exposure and information regarding subjects' disease severity. Patients enrolled in drug safety registries (N = 8,923) were excluded because their recruitment methods selected for a subset of patients with more severe RA than is ordinarily found in RA clinical practice, and their inclusion might have biased the study toward more severe RA patients. We used a random number generator to select a single questionnaire from each patient in the event a patient had completed more than one survey. Confidence intervals for the differences between groups in Table 1 were bootstrapped (i.e., utilized sampling of subsets with replacement to provide a more robust estimate than would be achieved by relying upon parametric assumptions). Differences between groups were assessed by logistic regression.

Corticosteroid use and relation to disease activity. In addition to estimating the cross-sectional prevalence of corticosteroids in RA, we used various regression methods to predict prevalent use at different levels of disease activity, including a HAQ score of 0 and PAS scores at remission (PAS $\leq$ 0.5) or MDA (PAS < 1.625). These analyses were carried out in an attempt to approximate the usage of corticosteroids attributable to the RA diagnosis, controlling for disease activity. The resulting associations were shown graphically in Figure 1 using a running line smooth of corticosteroid use on HAQ and PAS[17]. The line-smooth function uses local averaging of values to allow for an estimate of prevalence that is visually easy to interpret. Using population based expected ("normal") values for PCS and MCS in 14 age and sex specific categories[35], we also employed logistic regression analysis to estimate the probability of patients being treated with corticosteroids, had their PCS and MCS values been at the norm. To determine the normative PCS and MCS values for the age and sex groups, we used published population norms[35]. This method has been shown to be valid, using external validation[38]. Finally,

Table 1. Characteristics of 12,749 patients according to current* corticosteroid use.

	Corticosteroid, mean (SD) 4,523 (35.5%)	No Corticosteroid, mean (SD) 8,226 (64.5%)	Difference	95% CI
Age, years	60.8 (13.6)	60.3 (13.7)	0.5	(0.0, 1.0)
Sex, % male	25.1	22.3	2.9%	(1.5%, 4.3%)
College graduate, %	23.7	28.3	–4.6%	(–6.2%, –3.0%)
Non-Hispanic White, %	90.1	90.5	–0.4%	(–1.4%, 0.6%)
Total income, US dollars	42125 (27971)	45910 (29469)	–3785	(–4835, –2735)
Current smoker, %	17.5	14.4	3.1%	(1.5%, 4.6%)
Ever smoked, %	59.9	53.1	6.9%	(5.0%, 8.7%)
BMI	27.3 (6.4)	27.6 (6.4)	–0.3	(–0.5, 0.0)
Comorbid conditions, 0–11	2.6 (1.9)	2.4 (1.9)	0.2	(0.1, 0.3)
Duration of RA, years	15.6 (11.5)	15.4 (11.8)	0.2	(–0.2, 0.6)
Lifetime TJR, %	20.7	15.2	5.5%	(4.2%, 6.9%)
Died during followup, %	9.0	4.4	4.6%	(3.7%, 5.5%)
Social security disability, %	29.9	18.8	11.0%	(8.8%, 13.3%)
Lifetime DMARD/biologic use, count	3.0 (2.0)	2.1 (1.7)	0.9	(0.8, 0.9)
HAQ, 0–3	1.21 (0.75)	0.98 (0.73)	0.23	(0.20, 0.26)
Pain, 0–10	4.3 (2.8)	3.6 (2.8)	0.7	(0.6, 0.8)
Global severity, 0–10	3.9 (2.5)	3.3 (2.5)	0.6	(0.6, 0.7)
Patient activity score, 0–10	4.1 (2.2)	3.4 (2.2)	0.7	(0.6, 0.8)
Physical component score	30.0 (9.9)	34.1 (10.5)	–4.1	(–4.5, –3.7)
Mental component score	41.5 (14.1)	44.9 (14.0)	–3.4	(–3.9, –2.8)
EuroQol, US, 0–1	0.69 (0.18)	0.74 (0.17)	–0.05	(–0.06, –0.04)

*Use at a single randomly selected observation for each subject. BMI: Body mass index; TJR: Total joint replacement; HAQ: Health assessment questionnaire disability index; Pain: VAS pain scale; Patient global: VAS patient global severity scale; PAS: Patient activity scale; DMARD: Disease modifying antirheumatic drugs; SF-36 PCS: Short form 36 physical component scale; SF-36 MCS: Short form 36 mental component scale; See Materials and Methods for definition of DMARD or biologic treatment.

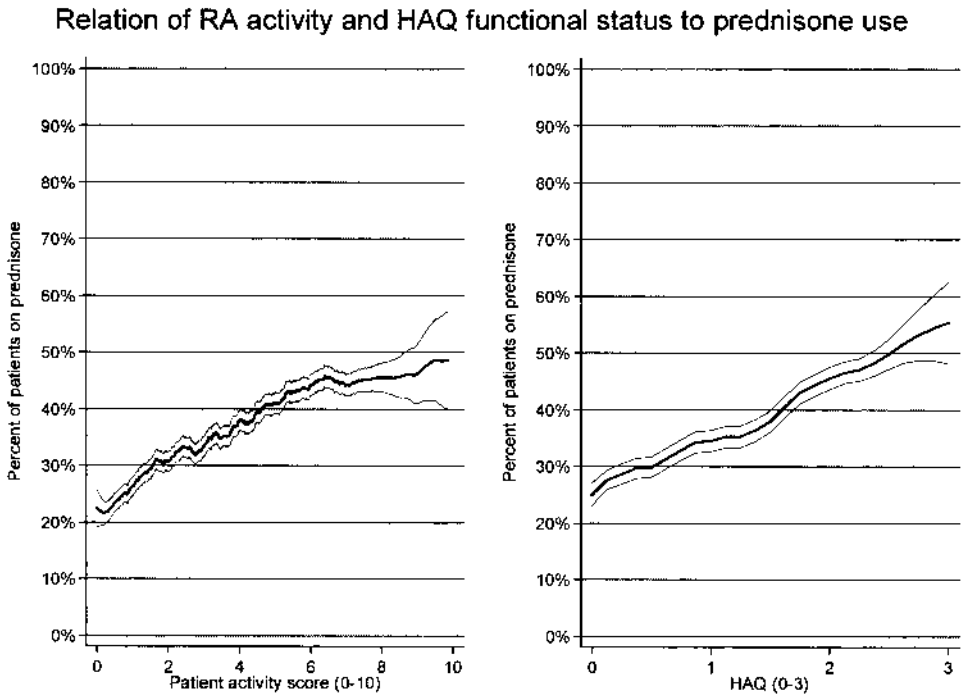

Figure 1. Prednisone use according to (A, left) RA activity and (B, right) HAQ functional status running line smoother, bounded by 95% confidence intervals.

we determined the prevalence of corticosteroid use in persons with NIRD as a further comparison group.

To illustrate the variation in corticosteroid prescribing patterns among providers, the association of corticosteroid use and disease activity in individual rheumatology practices was examined graphically (Figure 2). The Pearson correlation of this figure and the PAS and corticosteroid means were calculated using weights that accounted for the number of patients studied at each site, so that high volume contributors did not bias the results. The Figure 2 outset was an unweighted kernel density curve, which allows for a good visual representation of the distribution of prednisone use among practices (by eliminating discontinuous steps and removing the dependence of the plot upon arbitrary category cutpoints).

Corticosteroid use and association with disease outcome. The relation of duration of corticosteroid therapy to RA outcomes was examined graphically in Figure 3. The graphs were generated by running line smooths of the y variable on all x variable predictors simultaneously; that is, the value at each point on the plot was adjusted for all other covariates[17]. Using a simple type of backfitting, the resulting plot is a locally linear function of the predictors for each observation. In addition to these plots, logistic regression, adjusted for age, sex, duration of RA, and comorbidities, was used to estimate the percentage of patients with mortality during followup, current work disability, and total joint replacement (TJR). The results report the percentage for current corticosteroid users compared with non-current corticosteroid users (those with prior corticosteroid exposure, but who did not use corticosteroids during the last 6 mo period), as well as current users compared with patients who had never received corticosteroids.

Analyses of initiation and termination rates of corticosteroids in RA. All patients with RA were eligible for these analyses. The number of participants in these analyses is described in the Results section. Univariable and multivariable analyses of Table 2 were determined by Cox proportional hazards regression using time dependent covariates. Variables for HAQ, biologic exposure, and DMARD exposure were lagged 6 months in these analyses. That is, values obtained at the end of the previous 6-month assessment period were used to predict initiation or termination during the next 6-month assessment period. Variables were chosen for multivariable analysis after reviewing the univariable models and selecting variables of clinical and statistical importance. Goodness-of-fit of the analyses was determined using cumulative Cox-Snell residuals[39].

Our study was approved by the Via Christi institutional review board (IRB), Wichita, Kansas, USA. All participants signed an IRB approved informed consent.

Data were analyzed using Stata (College Station, TX, USA) version 9.1. Statistical significance was set at the 0.05 level, confidence intervals were established at 95%, and all tests were 2-tailed.

RESULTS

Disease severity and demographic differences among corticosteroid users and nonusers. At a randomly selected observation, we compared patients receiving corticosteroids with those not receiving corticosteroids. Patients receiving corticosteroids differed significantly in all variables except age ($p = 0.057$) and duration of RA ($p = 0.318$) compared with patients not currently receiving corticosteroids (Table 1). Among the striking differences were the percentage of patients who had had TJR (20.7% vs 15.2%) or were receiving US Social Security disability benefits (for subjects age < 62 yrs) (29.9% vs 18.8%) by the time of the randomly selected observation, and percentage of patients assessed at that observation who died during followup (9.0% vs 4.4%). These differences remained significant after adjusting for age and sex. Compared with those not taking corticosteroids, cor-

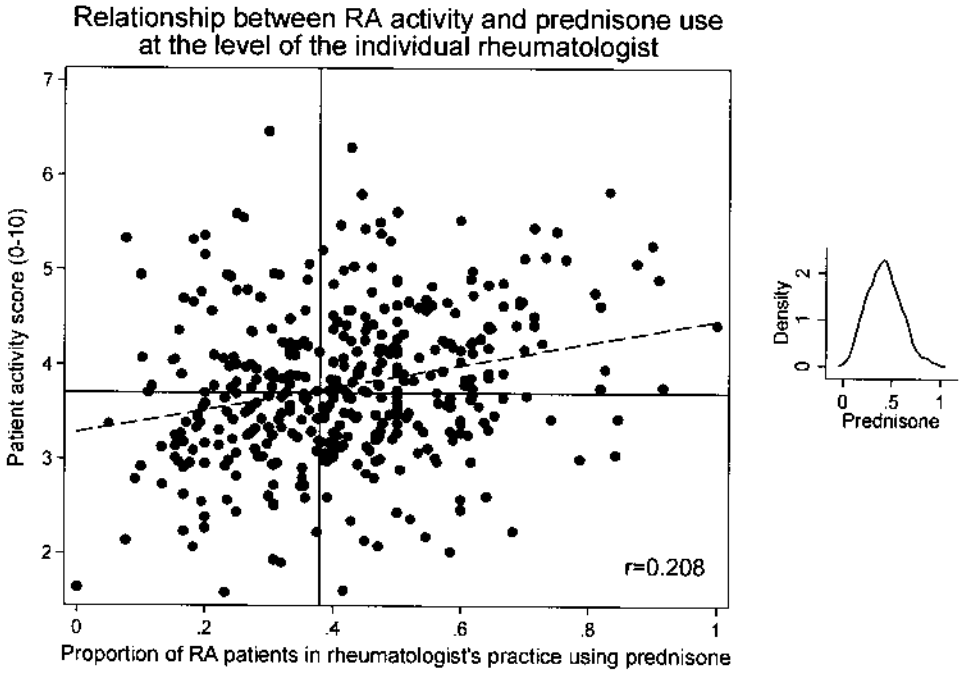

Figure 2. Relation between RA activity as measured by the Patient Activity Score (PAS) and prednisone use. Each point represents one of 407 rheumatology practices. PAS and prednisone values represent the average PAS and prednisone use in that practice. The vertical line divides the graph at the weighted proportionate mean of prednisone use by rheumatologist; the horizontal line (3.7) is at the mean of the PAS. The dashed line represents the regression of PAS on prednisone use. The outset graph (right) displays the distribution of prednisone use by individual practices.

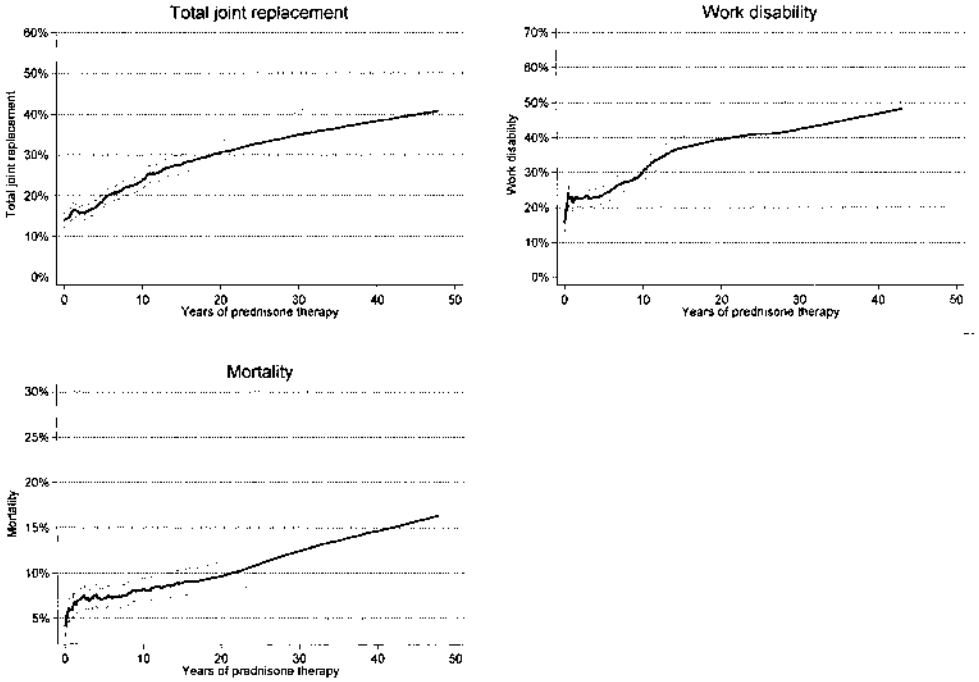

Figure 3. The association of duration of prednisone therapy in RA and the risk of total joint replacement, work disability and mortality. Analyses are adjusted for age, sex, comorbidity, and the duration of RA. Dashed lines represent 95% CI.

ticosteroid users had been treated with 0.9 more DMARD or biologics over their lifetime and had HAQ scores that were 0.23 units greater. In addition, they had more abnormal scores for PAS, pain, global severity, PCS, and MCS. Corticosteroid users also were 2.9% more likely to be male, 4.6% less likely to have been college graduates, and 3.1% and 6.9% more likely to be a current or lifetime smoker, respectively. Of interest, HAQ scores for those never treated with corticosteroids, those who received them in the past, and those currently receiving them were 0.98, 1.04, and 1.21, respectively. Therefore, it may be concluded that corticosteroid use is associated with increased disease activity, current and past smoking, and worse outcomes.

Corticosteroid use. For patients in these analyses, the current usage of corticosteroids was 35.5% (95% CI 34.6–36.3%) and lifetime use was 65.5% (95% CI 64.7–66.3%). To understand the rate of corticosteroid use among comparable patients who did not have RA, we examined 5,466 patients in the NDB who had no inflammatory rheumatic disease diagnosis (NIRD) at a randomly selected observation during the same period of enrollment. Adjusted to the age, sex, and number of comorbid conditions found in the patients with RA, 5.9% (95% CI 5.2-6.7%) of patients with NIRD were taking corticosteroids. Adjusted to a HAQ score of 0, the predicted percentage of NIRD patients taking corticosteroids was 3.9% (95% CI 3.1-4.8%).

The cross-sectional relation of corticosteroid use to RA activity. Figure 1A shows the relationship between the proportion of patients using corticosteroids and the RA disease activity as measured by the PAS. At PAS score of ≤ 0.5, which defines the remission level, the percentage taking corticosteroids was 21.3% (95% CI 18.8–23.7%), and a PAS score of ≤ 1.625, which corresponds to the Outcome Measures in Rheumatology Clinical Trials MDA definition, the percentage was 25.2% (95% CI 23.6–26.7%). At a HAQ score of 0 (Figure 1B) use of corticosteroids was 25.0% (95% CI 22.8–27.1%). We then modeled the percentage of patients expected to take corticosteroids if patients were at the average health status of the community. More precisely, in a regression analysis that included age, sex, PCS, and MCS, we predicted the percentage of patients that would be expected to take corticosteroids had their PCS and MCS been at age and sex based population norms. The model predicts corticosteroid use of 24.3% (95% CI 22.1–24.6%), which agrees with the estimates described above. Therefore, the range of estimates of corticosteroid use in RA defined by remission through MDA is 21.3–25.2%. Among patients in remission and with MDA the respective percentages receiving treatments were: DMARD 71.4% and 74.3%, biologics 18.2% and 18.8%, and DMARD or biologics 77.2% and 79.2%.

Use of corticosteroids among different rheumatologists: relation to disease activity. To understand physician corticosteroid prescribing behavior with respect to disease activity, we studied patients from 407 rheumatologists who contributed at least 10 patients to NDB surveys. We determined the mean corticosteroid use and PAS scores for patients of each of these rheumatologists. Figure 2 shows that the proportion of corticosteroid use varies substantially by rheumatology practice as well as being influenced by RA activity. The mean (standard

Table 2. Predictors of corticosteroid discontinuation and initiation

	Discontinuation		Initiation	
	Hazard Ratio	95% CI	Hazard Ratio	95% CI
Univariate predictors				
Age ≥ 65 years vs age < 65 years	0.87	(0.80, 0.95)	0.92	(0.83, 1.01)
Gender, male vs female	1.04	(0.94, 1.15)	0.91	(0.80, 1.02)
College graduate vs non-college graduate	1.12	(1.01, 1.23)	0.92	(0.83, 1.02)
Ethnic minority vs non-ethnic minority	1.01	(0.83, 1.23)	1.07	(0.90, 1.28)
Smoker vs non-smoker	0.96	(0.82, 1.12)	1.11	(0.97, 1.29)
Household income, $5,000 to $100,000 or more				
Quartile 1 (comparison group)	1.00		1.00	
Quartile 2	1.11	(0.97, 1.28)	0.99	(0.87, 1.12)
Quartile 3	1.14	(1.02, 1.28)	0.96	(0.83, 1.12)
Quartile 4	1.35	(1.19, 1.53)	0.85	(0.75, 0.98)
HAQ, 0–3, per unit increase*	0.82	(0.77, 0.88)	1.51	(1.40, 1.62)
Pain, 0–10, per unit increase*	0.97	(0.95, 0.98)	1.11	(1.09, 1.12)
Patient global, 0–10, per unit increase*	0.96	(0.94, 0.98)	1.11	(1.09, 1.13)
PAS, 0–10, per unit increase*	0.94	(0.92, 0.96)	1.16	(1.13, 1.18)
Biologic therapy vs no biologic therapy*	1.22	(1.11, 1.34)	1.29	(1.15, 1.45)
DMARD therapy vs no DMARD therapy*	1.12	(0.96, 1.30)	1.03	(0.91, 1.16)
SF-36 PCS per unit increase*	1.01	(1.01, 1.02)	0.97	(0.96, 0.97)
SF-36 MCS per unit increase*	1.01	(1.00, 1.01)	0.99	(0.98, 0.99)
Treatment groups				
No DMARD, no biologic* (comparison group)	1.00		1.00	
Biologic, no DMARD*	1.08	(0.81, 1.45)	1.34	(1.03, 1.74)
DMARD, no biologic*	1.09	(0.90, 1.31)	1.02	(0.89, 1.17)
DMARD and biologic*	1.36	(1.11, 1.66)	1.32	(1.12, 1.54)
Multivariable predictors				
Age ≥ 65 years vs age < 65 years	0.89	(0.80, 0.99)	0.84	(0.76, 0.93)
Gender, male vs female	0.96	(0.85, 1.09)	1.08	(0.95, 1.23)
College graduate vs non-college graduate	1.07	(0.95, 1.21)	1.00	(0.89, 1.12)
HAQ (lagged) 0–3 per unit increase	0.79	(0.73, 0.86)	1.46	(1.36, 1.57)
DMARD vs no DMARD (lagged)†	1.09	(0.92, 1.30)	1.03	(0.91, 1.16)
Biologic therapy vs no biologic therapy (lagged)‡	1.39	(1.22, 1.58)	1.34	(1.18, 1.53)

* Adjusted for age and sex. † Patients receiving biologic therapy were more likely to discontinue corticosteroids compared with patients receiving DMARD (H.R. 1.27 (95% CI 1.03 to 1.57, p = 0.027). ‡ Patients receiving biologic therapy were more likely to initiate corticosteroids compared with patients receiving DMARD (H.R. 1.30 (95% CI 1.08 to 1.57, p = 0.005). See Table 1 for definition of abbreviations.

deviation) of corticosteroid use for rheumatology practices was 0.38 (0.14). The correlation between mean PAS and mean corticosteroid use was 0.208.

Duration of corticosteroid use and RA outcomes. We examined the association of duration of corticosteroid therapy with 3 key RA outcomes. As shown in Figure 3, increasing duration of corticosteroid therapy was associated with a progressively stronger association for all adverse outcomes.

In a second series of analyses that were adjusted for age, sex, duration of RA, and comorbidities, the percentage of patients with the following outcomes was increased in current corticosteroid users compared with non-current (prior) corticosteroid users: mortality 5.7% (95% CI 5.1–6.5%) versus 2.6% (95% CI 2.3–3.0%), work disability 28.4% (95% CI 26.6–30.3%) versus 17.2% (95% CI 16.1–18.3%), and TJR 18.5% (95% CI 17.4–19.8%) versus 13.0 (95% CI 12.2–13.8%, data not otherwise shown).

We also characterized the association between RA outcome and corticosteroids in another way: by measuring the risks associated with past corticosteroid therapy and current corticosteroid therapy, compared with risks in the 34.5% of patients who had never received corticosteroids. Adjusted for age, sex, duration of RA, comorbidity, and lifetime count of DMARD and/or biologics, prior corticosteroid exposure was not associated with risk of mortality [odds ratio (OR) 1.2 (95% CI 0.9–1.5), p = 0.170], while current corticosteroid use was associated with mortality [OR 2.2 (95% CI 1.9–2.7), p < 0.001]. With regard to work disability, the respective OR were 1.6 (95% CI 1.4–1.8), p < 0.001 and 2.3 (95% CI 2.0–2.6). For TJR the respective associations were OR 1.4 (95% CI 1.2–1.5), p < 0.001 and 1.7 (95% CI 1.5–1.9), p < 0.001.

Discontinuation and initiation of corticosteroids. To determine the risk of corticosteroid discontinuation and its predictors, we studied 4,731 patients who were receiving cortico-

steroids at the time of their NDB first assessment. As a portion of their corticosteroid exposure occurred prior to enrollment in the NDB, we termed this subset the "left censored" cohort. Of these, 2,098 discontinued corticosteroids during 8,648 patient years of followup. As illustrated in Figure 4A, the median time to corticosteroid discontinuation was 3.0 years (95% CI 3.0–3.5 yrs), and the annual incidence of discontinuation was 24.3% (95% CI 23.2–25.3%).

We studied discontinuation rates separately for patients who were not receiving corticosteroids at the first NDB assessment, but who subsequently began that therapy during the period of prospective participation in the NDB (Figure 4B, "New starts"). For the 1,624 patients who contributed 4,250 observations (1,624.3 patient-years of followup), the rate of discontinuation was greater than in the left censored group shown in Figure 4A. The median time to discontinuation was 1.0 year (95% CI 1.0–1.0), and the annual rate of discontinuation was 56.9% (95% CI 53.4–60.7%).

Figure 4C shows the rate of initiation of corticosteroids for 8,122 patients who were not receiving corticosteroids at the time of their first questionnaire assessment. During 19,231 patient-years of observation, the corticosteroid initiation rate was 8.9% (95% CI 8.4–9.3%) per year, and 25% of patients started corticosteroids by 3.5 years of observation.

Predictors of discontinuation and initiation. Additional analyses (Table 2) were conducted for the 4,731 patients in Figure 4A using Cox proportional hazards regression with time-dependent covariates. Longer duration of corticosteroid use (or being less likely to discontinue corticosteroids) was associated with being older than 65 years, not being a college graduate, having a lower household income, and with having more abnormal HAQ, pain, global, PAS, and SF-36 PCS and MCS scores (Table 2). Patients receiving biologics terminated corticosteroid therapy more rapidly than those not receiving biologics. We also studied these variables in a parsimonious multivariable model (Table 2). The data of the multivariable predictive analyses show that lower disease activity and treatment with biologics was associated with corticosteroid discontinuation, as was age less than 65 years.

For patients initiating corticosteroids during the period of NDB followup (Figure 4C) results were similar with respect to the effect of HAQ, pain, global, PAS, and SF-36 PCS and MCS scores, and of biologics in the univariate analyses (Table 2). However, only household income was a significant predictor of initiation among demographic variables. In the multivariable analysis (Table 2), predictors were generally the same for initiation and discontinuation, except that the hazard ratios were reversed. A history of biologic use was the exception to this trend, as those with exposure to biologics

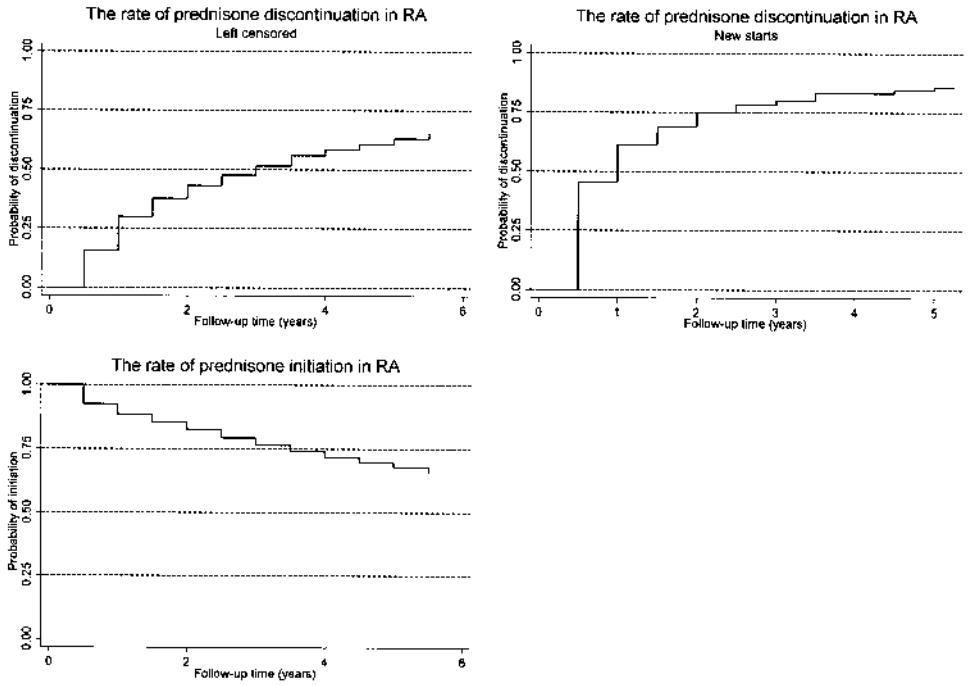

Figure 4. A. (upper left): the estimated probability of discontinuing prednisone among 4,731 RA patients who were receiving prednisone at the time of first assessment (i.e., "left censored"). The median time to discontinuation was 3 years. B. (upper right): the estimated probability of discontinuing prednisone among 1,624 RA patients who were not receiving prednisone at the time of first assessment, but subsequently started that treatment. The median time to discontinuation was 1 year. C. (lower left): the estimated probability of starting prednisone among 8,122 patients who were not receiving prednisone at the time of their first questionnaire assessment. The prednisone initiation rate was 8.9% (95% CI 8.4–9.3%) per year.

were more likely to have initiated, as well as discontinued corticosteroids.

DISCUSSION

Chronic corticosteroid use has the quality of a mystery. Physicians and patients clearly value corticosteroids, as 35.5% of the 12,749 patients with RA in this report use corticosteroids and 65.5% have received it over their lifetimes (Table 1). In addition, 8.9% of patients not taking corticosteroids begin corticosteroid treatment each year and 25% of such patients will have received corticosteroids after 3.5 years of observation.

Still, corticosteroids have readily-recognized side effects, including side effects that annoy patients such as weight gain, bruising, and edema, as well as serious side effects that can lead to disability or death, including osteoporosis, cataracts, diabetes, cardiovascular disease, and infection[1,9-15]. The potential costs of adverse effects may be substantial[40] and have led to calls to address the safety and toxicity of rheumatic therapies systematically[2].

Current corticosteroid users in this study had more severe RA (Table 1), had a greater likelihood of current and past smoking history, and worse outcomes compared with past users and corticosteroid naïve patients, although these associations do not necessarily imply causality. Particularly of interest is the increased risk of mortality (9.0 vs 4.4%), work disability (29.9% vs 18.8%), and TJR (20.7% vs 15.2%). Outcomes worsened further with duration of use (Figure 3).

Although the data show that corticosteroid use is associated with important adverse outcomes, it is difficult to determine the extent to which these associations are causal, as RA disease activity and severity and corticosteroid use are severely confounded. In addition, the longterm associations also suffer from problems of left-censoring. However, there is evidence that links corticosteroids to serious adverse effects in less narrowly defined populations, suggesting that these associations (whether causal, or not) are not restricted to RA[18,41,42]. To determine the true effect of corticosteroids on RA outcomes, relevant, detailed covariates must be collected over the entire course of RA. However, this is close to an impossible task, given the long duration of RA and the fact that patients are rarely observed quantitatively and carefully over its course.

Good quality evidence from biologically-based observational investigations and from basic mechanistic studies suggests that corticosteroids may contribute to morbidity, at least with respect to the most intensely studied outcome, osteoporosis[43-45]. In addition, observational data indicate that rates of fracture are associated with exposure to even low-dose oral corticosteroids and normalize with discontinuation of these agents[46,47]. Of course, even with regard to osteoporosis, there is some evidence to the contrary — namely, that corticosteroids may decelerate RA-related bone loss[48,49].

One might conclude that prescription of corticosteroids occurs when the presumed benefits outweigh the disadvantages in the minds of physicians and patients. However, different physicians may not assess benefit and risk similarly, and this can be further complicated by the fact that benefits tend to be immediate while adverse effects can occur in a distant future. In their study of 50 physicians and 468 patients, Criswell and Henke have shown that characteristics of physicians' training and experience explain the differential propensity to prescribe corticosteroids more or less frequently[19]. In their study, performed in 1990, corticosteroids were prescribed to 53.7% of patients compared with the 35.5% prevalence noted in the current study.

In agreement with Criswell and Henke, Figure 2 (outset) shows that the percentage of patients using corticosteroids in individual physicians' practices follows a generally normal distribution, such that there are high and low percentage users of corticosteroids among rheumatologists. This might have been predicted in view of the debate regarding corticosteroid use[50,51].

Given the confounding with physician personal preference, it is fair to ask what non-physician factors are associated with corticosteroid use and discontinuation. As shown in Figure 1 and Table 2, persons with worse clinical status, as measured by the HAQ and PAS, are more likely to receive corticosteroids, and patients with better clinical status are more likely to discontinue that therapy. Biologics are associated both with initiation and discontinuation of corticosteroids. It seems likely that corticosteroid initiation occurs because biologics are more often prescribed to patients using corticosteroids or, stated differently, that the reason for initiating biologics is the same reason as for initiating corticosteroids. The reason that biologics are associated with corticosteroid discontinuation is not immediately clear. It is possible that physicians use the clinical improvement associated biologic therapy as an opportunity to discontinue corticosteroids or as an opportunity to exchange one drug (steroids) for another (biologics), or even that they are concerned with possible increased risks associated with the simultaneous use of both agents. It is also of interest that physicians are less likely to prescribe corticosteroids to patients over the age of 65 years, but that once prescribed, such patients are more likely to continue corticosteroid therapy.

Using a variety of methods, we observed that 21.3% to 25.2% of RA patients with limited RA activity (remission through MDA) were currently taking corticosteroids compared with 35.5% of all patients who used this treatment. The use of low dose corticosteroids (median 5 mg per day of prednisone) in patients who are doing very well supports the notion that under certain circumstances, physicians may rely upon corticosteroids for their disease-modifying effects, rather than for symptom management. Alternatively, there may be some decisional inertia or apprehension on the part of the physician and patient.

The data presented regarding rates of prednisone initiation and discontinuation (Figure 4) are consistent with published

data[21,22,52]. Our data more specifically illustrate that with the passage of time, discontinuation is less likely (i.e., the curve flattens), and about one-third of patients using corticosteroids appear to be persistent users. As these observations are left-censored (consisting of patients already taking corticosteroids), we also examined patients newly starting corticosteroids (Figure 4B). Again, the data support the suggestion that rates of discontinuation diminish with time.

Thus, the above results suggest that there are 2 populations of corticosteroid users, those who discontinue corticosteroids relatively quickly and a smaller group of persistent users. There also appears to be a continuous turnover of corticosteroid use, turnover that appears to reflect RA activity (Table 2).

In summary, lifetime use of corticosteroids is approximately 65.5%. Cross-sectional use is 35.5%. About one-third of patients may be persistent corticosteroid users, but most use of corticosteroids is for the short term. Corticosteroid users have increased disease activity and more severe RA outcomes. Initiation and discontinuation of corticosteroid therapy is predicted by disease activity, but 21–25% of patients with MDA also use corticosteroids. The simple idea of "once on corticosteroids — always on corticosteroids" is incorrect and applies to only a minority of patients.

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