Can Severity Be Predicted by Treatment Variables in Rheumatoid Arthritis Administrative Data Bases?

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ABSTRACT. ***Objective.*** Administrative data bases provide rapid access to data regarding treatment and morbidity of rheumatoid arthritis (RA). A serious limitation of administrative data bases is the lack of information regarding RA severity, as in the case of lymphoma, where RA severity may contribute to the cause of the adverse outcome. We examined whether treatment variables could predict RA severity.

Methods. We studied 7541 patients with RA who were participating in a longitudinal study of RA outcomes. Disease severity was determined by the Patient Activity Scale (PAS), which represents on a 0 to 10 scale the mean of 0–10 standardized values of pain (by visual analog scale), patient global severity, and the Health Assessment Questionnaire. We tested the ability of disease modifying antirheumatic drugs (DMARD) and biologic treatment variables and the lifetime number of these treatments to predict severity status. The receiver-operating characteristic (ROC) area under the curve (AUC) was used to describe the association between severity and treatment variables.

Results. There was little difference in PAS scores between various treatments and treatment groups, including scores of the 18.3% of patients receiving no DMARD or biologic therapy. The ROC AUC to distinguish PAS scores above and below the median was 0.64 (60.5% correctly classified) and was 0.70 (67.2% correctly classified) in distinguishing first compared to fourth quartiles PAS scores.

Conclusion. Treatment variables do not accurately or usefully identify severity status. As a corollary, there is little difference in severity between patients receiving different treatment regimens, and actual measures of severity rather than treatment surrogates are required to assess RA severity. (First Release Sept 1 2006; J Rheumatol 2006;33:1952–6)

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

Administrative data bases provide rapid access to data regarding treatment, compliance, and morbidity[1-10], and have been used in patients with rheumatoid arthritis (RA)[1,11-15]. Such data may be valuable in establishing links between RA, RA treatment, and adverse outcomes[1,15-18]. A serious limitation of administrative data bases is the lack of information regarding RA severity, for it is often the case, as for example with lymphoma, that RA severity rather than RA treatment may contribute to the cause of the adverse outcome. We investigated whether the choice of treatment(s) and past treatments might be useful in identifying severity classes among patients with RA. If this were the case it would enlarge considerably the usefulness of administrative data bases.

To assess severity, we used the Patient Activity Scale (PAS)[19]. Composed of the Health Assessment Questionnaire (HAQ), a visual analog scale (VAS) for pain, and a global severity VAS, the scale is reported on a 0–10 scale, and is strongly correlated with disease activity and severity[19].

MATERIALS AND METHODS

Patients in this study were participants in the National Data Bank for Rheumatic Diseases (NDB) longitudinal study of RA outcomes. NDB participants are recruited on a continuing basis from the practices of United States rheumatologists, and are followed prospectively with semiannual, detailed, 28-page questionnaires, as described[20-23]. In this report we studied 7541 patients with RA who had completed at least one semiannual questionnaire concerning the period between January 1, 2002, and December 30, 2004, and who were not participants in a safety registry. Safety registry patients were excluded because their recruitment methods select 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. We used data starting in 2002 to avoid biasing results toward severity by including patients receiving biologic therapy shortly after introduction of that therapy. In this report 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.

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Supported by a grant from Bristol-Myers-Squibb. During its existence, the National Data Bank for Rheumatic Diseases has received funding support from pharmaceutical companies including Merck, Pfizer, Tap, Wyeth-Australia, Aventis, Novartis, Bristol-Myers Squibb, Amgen, and Centocor.

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Accepted for publication May 11, 2006.

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

At each assessment we recorded demographic variables and treatments. To determine lifetime use of disease modifying antirheumatic drugs (DMARD) and/or biologics, patients report all treatments used on entry into the longitudinal study, and these treatments are updated with all subsequent questionnaires. Biologic therapy consisted of infliximab, etanercept, adalimumab, and anakinra. Patients report functional status using the HAQ[24,25]. We also determined pain, global severity, and fatigue using VAS[26]. The VAS scale measures 21 points, from 0 to 10 at 0.5-unit intervals. The PAS is calculated by multiplying the HAQ by 3.33 and then dividing the sum of the VAS pain, VAS global, and HAQ/HAQ-II by 3. This yields a 0–10 scale[19].

The mood scale used in this report represents the normalized Arthritis Impact Measurement Scales (AIMS) anxiety and depression scales if available[27]; otherwise, it represents the Medical Outcomes Study Short Form-36 (SF-36) Mental Health subscale[28]. Both scales are transformed to a 0–10 scale, with higher values representing greater mood abnormality. Lin's concordance correlation coefficient[24] for the 2 scales in 21,982 patients was 0.860 (95% CI 0.856 to 0.863), indicating a very high degree of concordance.

Statistical methods. In addition to the descriptive data of Figures 1 to 3, we measured the ability of treatment variables to predict PAS severity in 2 ways, first, to predict patients greater than or equal to median, and second, to predict patients in the fourth quartile compared to the first quartile. The area under the receiver operating characteristic (ROC) curve was calculated for these analyses as was the percentage correctly classified. Comparisons between groups were analyzed by t tests and chi-square analysis, as appropriate. Data were analyzed using Stata (Stata Corp., College Station, TX, USA) version 9.1.

RESULTS

In these analyses, we first describe PAS scores according to treatment groups so that the relation between treatment and RA activity may be seen. Then we analyze the ability of treatment variables to predict the median PAS.

The mean age of the 7541 study participants was 60.8 (SD 13.4) years and the median duration of RA was 14.6 years. Women made up 78.0% of the study population. The mean (SD) and median of the PAS was 3.5 (2.2) and 3.4. As shown in Figure 1, the greatest median PAS scores were found in patients not receiving DMARD or biologics, 3.7 (interquartile range 1.7–5.7), and those using DMARD and biologics, 3.7 (IQR 2.0–5.4). The smallest PAS occurred in patients using DMARD alone: 3.1 (IQR 1.5–4.9). The use of prednisone, while not altering the rankings, is associated with greater PAS scores. The percentages of patients using various drug combinations were as follows: no DMARD or biologic, 18.3%; using a DMARD, 74.2%; using a biologic, 33.1%; and using a biologic and/or a DMARD, 81.7%.

Figure 2 illustrates these data for individual treatments. The percentage using the drugs (shown in parentheses in Figure 2) is greater than 100% because patients could be taking more than one treatment at a time. Among drugs that were commonly used, prednisone had the highest (4.1) and hydroxychloroquine the lowest (3.0) PAS median score. Among patients not using DMARD or biologics the median PAS was 3.7.

We also examined the effect of the lifetime number of DMARD or biologic used on PAS scores, as illustrated in Figure 3. Scores generally increase with number of DMARD or biologics. However, a relatively high score for nonusers of DMARD or biologics was noted, 3.8.

We constructed 2 models to assess the ability of individual treatment variables and age, sex, and RA duration to predict PAS scores. In the first model, we assessed the predictive abil-

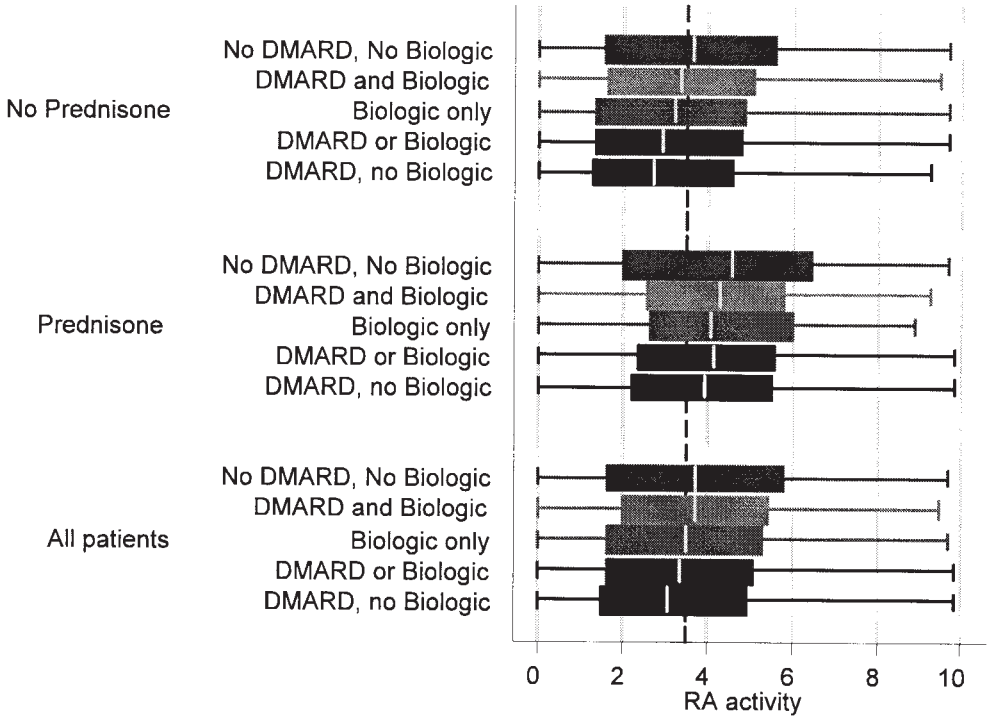

Figure 1. PAS scores among 7641 patients with RA according to current general treatment groups. *The vertical line indicates the median PAS score of all patients.

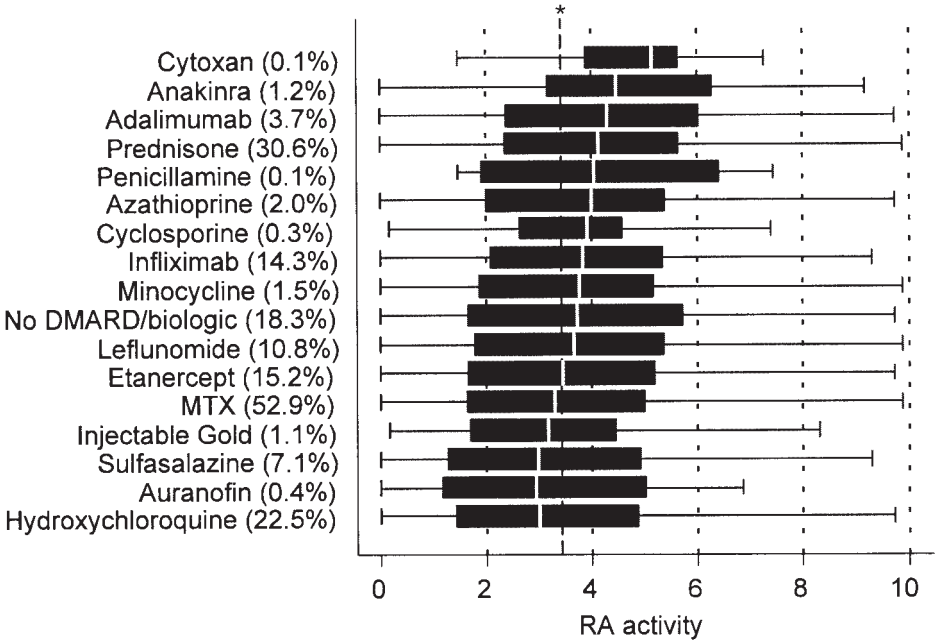

Figure 2. PAS scores among 7641 patients with RA according to current specific treatment groups. Data in parentheses are percentages of patients receiving that treatment. The groups are not mutually exclusive. *The vertical line indicates the median PAS score of all patients.

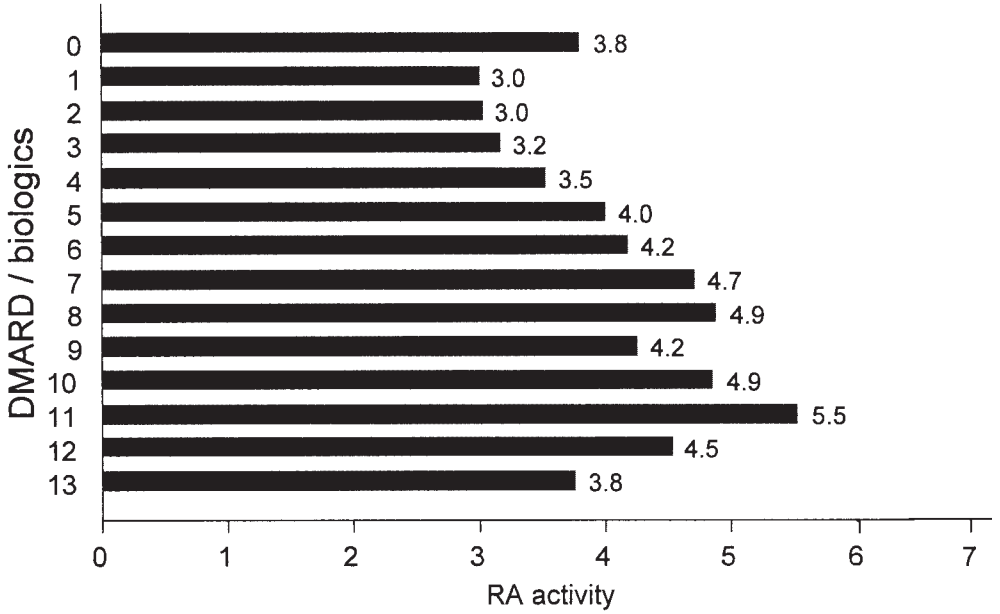

Figure 3. Median PAS scores according to number of lifetime DMARD and/or biologics.

ity of treatment variables to identify PAS scores above the median compared with PAS scores below the median. In this model we used logistic regression to predict PAS group using all DMARD and biologic treatments, the lifetime number of DMARD or biologics, and age, sex and RA duration. The area under the ROC curve was 0.64 for the model, and the percentage correctly classified was 60.5% (Figure 4).

In the second model we used these variables to predict membership in the fourth quartile of PAS compared with the first quartile, effectively identifying the most extreme groups. In this model the area under the ROC curve was 0.70 and the percentage correctly predicted was 67.2% (Figure 4).

To gain further understanding of the PAS results in nonusers of DMARD or biologics, we explored the distribution of lifetime DMARD and biologics for patients who were not currently using these treatments, and also examined the PAS scores (Table 1). For the 24.3% of patients who had used only one DMARD or biologic, the mean PAS was 3.4, com-

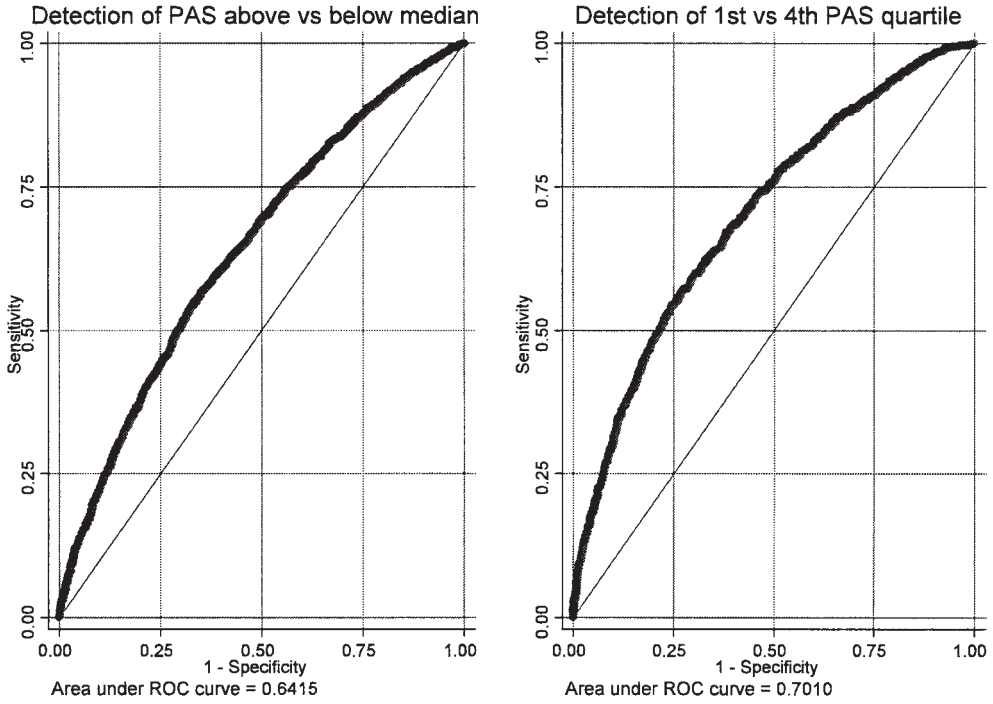

Figure 4. ROC curves for the ability of DMARD and biologic treatments, lifetime number of DMARD or biologics, and age, sex and RA duration to detect PAS scores above vs below median (left) and PAS first vs fourth quartiles (right).

Table 1. Lifetime DMARD use and Patient Activity Scale (PAS) scores among current nonusers of DMARD and biologics.

Lifetime DMARD or Biologics (no.)	PAS mean (SD)	No. of Patients
0	3.8 (2.4)	621
1	3.4 (2.3)	336
2	3.9 (2.5)	182
3	3.5 (2.4)	102
4	4.0 (2.4)	67
5	5.1 (2.2)	42
6	6.2 (2.1)	17
7	4.9 (2.3)	10
8	7.7 (0.4)	4
12	5.8 (0.0)	1
Total	3.8 (2.4)	1382

pared with 3.5 in the entire sample. For all other values of lifetime DMARD or biologics, these current nonusers had higher PAS scores compared with the sample as a whole.

Current nonusers of DMARD and/or biologics were compared with users. The groups did not differ by sex ($p = 0.147$), but users were more likely to be ethnic minorities (23.4% vs 17.6%; $p < 0.001$), college graduates (20.3% vs 17.5%), and to have more fatigue (4.6 vs 4.2; $p < 0.001$) and higher (more abnormal) mood scores (2.9 vs 2.6; $p < 0.001$). The groups did not differ in age ($p = 0.359$) or duration of RA ($p = 0.490$).

DISCUSSION

Our data show that there is little difference in severity scores according to treatment, and that lifetime use of DMARD/biologics and demographic variables do not identify severity groups that can be distinguished clinically with adequate sensitivity and/or specificity, as values for the area under the ROC curve of 0.64 and 0.70 for the 2 analyses are unsatisfactory. In addition, we found that nonusers of DMARD and biologics had higher PAS scores than users. Most (55%) current nonusers of DMARD and nonsteroidal antiinflammatory drugs had been prior users of DMARD or biologics. Finally, we found that prednisone users had the highest PAS scores.

These data indicate that treatment variables cannot be used to classify patients according to severity. This would argue against using such variables that are available in administrative data banks for severity classification.

In addition, the finding of higher PAS scores in patients not being treated with DMARD or biologics argues strongly that such patients do not have milder RA. Therefore using a classification of "No DMARD/biologics," "DMARD," and "biologics" as indicators of severity and perhaps, therefore, for risk of side effects, is not supported by the data. We note as well that prednisone is the primary marker for severity.

The data of our study represent, to an unknown extent, confounding by indication. They should not be interpreted to show superiority of one treatment compared to another. However, they may offer some insight to prescription behavior by physicians and patients (Figure 2). Hydroxy-

chloroquine, for example, has the lowest PAS score, and that result could suggest that it was not felt necessary to advance to more aggressive treatments. The same case could be made for methotrexate.

In summary, treatment variables do not provide a basis for classification of RA severity, and patients not currently undergoing DMARD/biologic treatment have the highest level of severity.

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