Editorial

Measuring the Efficacy and Effectiveness of Rheumatoid Arthritis Therapy: Time to Change Our Thinking and Adopt a New Model

In the current issue of *The Journal*, Kremers and colleagues document a half-century of rheumatoid arthritis (RA) treatment in a retrospective population-based inception cohort of patients from Rochester, Minnesota[1]. The methods, analysis, and data presentation are extraordinarily well done, as we have come to expect from Prof. Gabriel's group.

Although well documented in this unique data set, the news from this report is not new: treatment with disease modifying antirheumatic drugs now begins earlier in the course of RA, patients with more severe RA receive earlier and more aggressive treatment, and methotrexate (MTX) is now the most common RA treatment. The authors argue that their data "provide evidence for the translation of scientific evidence into clinical practice in rheumatology." This assertion, however, raises the interesting and vital question as to what should be considered "scientific evidence" in regard to treatment practices. We would argue that the proof for the effectiveness of practice changes in RA must come from improved results that are causally related to practice changes. What often passes for scientific evidence comes from several sources: the results of some randomized clinical trials (RCT), the promulgation of such results by industry and paid "thought leaders," and the consequent trends in beliefs of physicians and physician-educators.

In the last 5 years there has been a major revolution in the therapy of RA, particularly with the introduction of anti-tumor necrosis factor (TNF) therapy with etanercept, infliximab, and adalimumab (Figure 1). RCT have demonstrated remarkable inhibition of radiographic progression and high levels of response to therapy as measured by criteria of the American College of Rheumatology for response ACR20, 50, and 70, as well as by the Disease Activity Score[2-9]. Despite these exciting results, we have few independent data regarding intermediate and longterm effectiveness of these treatments. Such data are critical if we are not to repeat the pattern of documenting use, but never fully understanding efficacy, costs, and cost-effectiveness or cost-utility[10].

In Figure 1, we present a model of how to assess treatment patterns and at the same time measure and model cost and effectiveness. The data from this figure come from 2928 patients with RA followed in the National Data Bank for Rheumatic Diseases (NDB). Each patient completed at least 9 of 11 semiannual assessments over a 5.5-year period. Several important trends can be seen. Corticosteroid and nonsteroidal antiinflammatory drug (NSAID) use decreased by about 10%, while anti-TNF therapy use rose from 5% to 30%. Of particular interest, the percentage of patients with Health Assessment Questionnaire (HAQ) scores > 1 increased from about 50% to about 53%. As HAQ is known to increase with age and RA duration, we note that the increase observed is less than expected, based on published rates of HAQ increase over time. From data like these, changes in function and quality of life in the general population of RA patients can be measured, and true estimates of costs and utilities obtained.

If, as we have recently demonstrated in preliminary reports, prednisone use in RA is causally related to infection, diabetes, and cardiovascular and cerebrovascular events[11-13], the decreased use of prednisone (and NSAID) shown in Figure 1 is encouraging. NDB analyses also indicate that the apparent prognosis of patients not treated with anti-TNF therapy improves as patients with more severe illness switch to anti-TNF therapy and thereby "improves" the status of those not taking anti-TNF treatment. The data from Figure 1, other NDB data, and the report from the Mayo Clinic group also underscore the imperative that observa-

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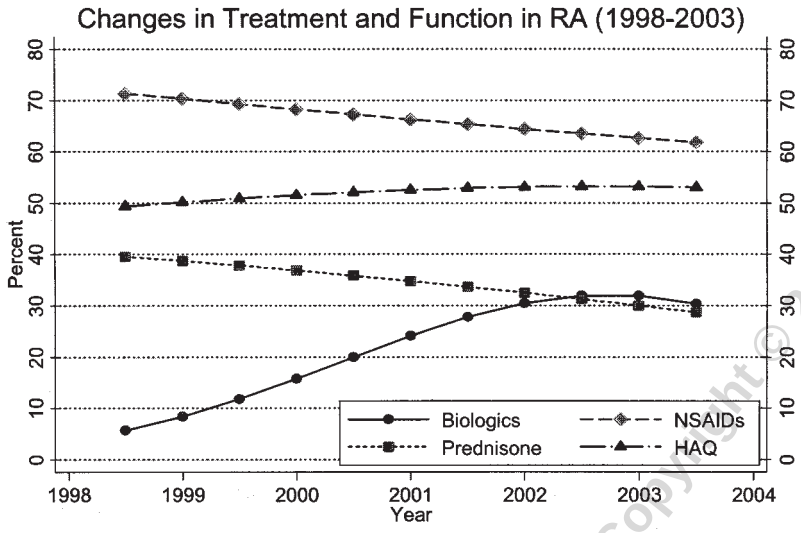

Figure 1. Treatment changes and functional outcome in RA from 1998 through 2003. Data from 2928 patients with RA followed in the National Data Bank for Rheumatic Diseases (NDB). Each patient completed at least 9 of 11 semiannual assessments over a 5.5-year period. Percentages refer to the percentage of patients receiving biologics (etanercept, infliximab, and adalimumab), NSAID, and prednisone at the 11 semiannual assessment periods. HAQ represents the percentage of patients with HAQ scores > 1. Data are modeled and smoothed for easier viewing and interpretation.

tional outcome data must include all patients, not just those receiving treatments that are current or momentarily of interest.

How shall vital, informative treatment and outcome data be obtained — that is, data that can really answer questions regarding effectiveness and costs? We believe that longitudinal data banks can be the answer. During the timeframe represented by Figure 1, multiple large experimental studies of coxibs and biologics have been undertaken at enormous costs, and often with conflicting, noncomparative answers. The cost of just one of these studies would be sufficient to fund a large outcomes data bank for a decade or more.

Administrative databases have been used effectively to identify adverse effects[14,15]. Programs such as the US Women's Health Study are also effective models[16]. Properly constituted, rheumatology-specific data banks are capable of more detailed answers than prospective randomized trials, particularly regarding effectiveness and cost-effectiveness. The pharmaceutical industry has something to gain and perhaps something to lose with data bank research. Safety data from longitudinal data banks can protect industry from the enormous costs and bad publicity related to rare chance events by providing proper denominators of exposure[17,18]. In addition, proper identification of adverse events is in industry's and the public's best interest. Where industry may not do as well is with regard to efficacy. Clinical trials are designed to maximize efficacy, while data banks are neutral in that respect. However, data bank research clearly demonstrates treatment efficacy, although that efficacy is likely to be less striking when compared to marketing-driven research.

It is well known that observational studies have important limitations in regard to causal associations, primarily because of nonrandom prescription of treatments. These limitations can be largely overcome provided all relevant covariates are collected repeatedly, for all patients, prior to the introduction of new therapies. Our understanding of how to conduct observational studies has increased dramatically in the last decades. Although data from RCT are often claimed to represent the best evidence, the literature suggests that prospective observational nonrandomized studies produce results very similar to those of RCT[19-21]. In addition, results from observational studies increasingly are providing vital information of signal public health interest that have not been obtained through the RCT model.

Kremers and colleagues' elegant description of the last 50 years of RA care and its measurement should be replaced by a new model of prospective, cooperative data collection and analysis that directly addresses issues of clinical and public health interest.

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