Longitudinal Cohort Studies

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ABSTRACT. Rheumatological disorders are complex conditions characterized by a variety of clinical manifestations and courses in different patients with the same condition. The best way to understand the course and prognosis of these patients is through longitudinal observational cohort studies. Such studies have been facilitated by computer technology that allows tracking of large numbers of patients and visits and analysis of a large amount of data. There are requirements for such datasets to be informative: internal and external consistency; clearly defined methods of observation and measurement; complete followup; consideration of potential confounders. We describe the usefulness of an observational cohort analysis using the University of Toronto Psoriatic Arthritis Clinic Database as a model. Analysis issues are highlighted and proposed mechanisms offered for keeping patients involved to ensure complete followup is maintained.

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Rheumatological disorders are complex conditions characterized by a variety of clinical manifestations and courses in different patients with the same condition. The best way to understand the course and prognosis of these patients is through longitudinal observational cohort studies. Longitudinal cohort studies are dependent on prospective collection of data on a large number of patients followed according to standard protocols. These protocols include clinical features, laboratory assessments, radiological evaluation, and genetic information. By definition longitudinal cohort studies require prolonged periods of observation of a large number of patients to observe the varied clinical presentations and clinical course, as well as outcome. Such studies have been facilitated by computer technology, which allows tracking of large numbers of patients and analysis of large amounts of data

Longitudinal cohort studies allow us to describe disease course and record longterm complications of the disease and its therapy. They also allow us to study association between course and drug therapy, and identify predictors of response or resistance to therapy, as well as drug toxicity. Moreover, they help us better understand the pathogenesis of a disease and the mechanisms of disease progression. Information derived from such studies can help in the design of future drug trials.

CHARACTERISTICS OF A LONGITUDINAL DATABASE

An essential requirement for use of a longitudinal dataset in the study of prognosis is internal and external validity of the cohort collected. In other words, the patients should be representative of the population from which they are drawn such that they can be considered a random sample, and selection bias is avoided. The methods of observation must be clearly defined and the measurement tools must be valid and reliable. Complete followup is important to avoid information bias. Potential confounding factors such as time and intervention need to be considered, and may be overcome by design and analysis.

The University of Toronto Psoriatic Arthritis Clinic at the Centre for Prognosis Studies in the Rheumatic Disease, Toronto Western Hospital, provides an example of longitudinal observational cohort studies. This clinic was initiated in 1978 to study the course and prognosis of patients with psoriatic arthritis, an inflammatory arthritis associated with psoriasis, usually seronegative for rheumatoid factor. Patients are followed at 6–12 month intervals according to a standardized protocol that includes clinical and laboratory information at each visit, patient derived instruments such as the Health Assessment Questionnaire (HAQ), Medical Outcome Survey Short Form 36 (SF-36) and a fatigue scale once a year, and radiological evaluation every 2 years.

The methods of evaluation and measurements performed in the clinic have been shown to be reliable: Physicians attending the clinic assess joint activity and damage in the same way[1]. The radiological scoring method used, a modification of the Steinbrocker technique, has also proven reliable and sensitive to progres-

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sion of damage over time[2]. The patient derived questionnaires have also been validated in our clinic[3-5]. All information collected on these patients is entered onto an ORACLE database. There are now 657 patients registered in the database:

Total number of patients	657
Male (%)	56
Female (%)	44
Mean age of onset of psoriasis (years), ± SD	29 ± 14
Mean age of onset of PsA (years), ± SD	36 ± 13
Age at last visit (years), ± SD	51 ± 14
Mean duration of psoriasis (years), ± SD*	22 ± 13
Mean duration of PsA (years), ± SD*	15 ± 10
Mean number of actively inflamed joints, ± SD*	6 ± 9
Mean number of clinically deformed joints, ± SD*	9 ± 13

*At presentation

ILLUSTRATIVE FINDINGS

This database has allowed us to demonstrate that psoriatic arthritis (PsA) is more severe than previously thought. We found that 20% of patients have severe disease, with deformities, radiological damage, and functional disability[6]. Clinical damage progresses over time such that 55% of the patients who have been observed for more than 10 years have more than 5 clinically damaged joints[7]. We have also been able to identify predictors for progression of clinical damage. Patients with 5 or more swollen joints at presentation to clinic, those who have been treated with higher levels of medication and with corticosteroid therapy, are at increased risk for progression of clinical damage[8]. The number of actively inflamed joints at each visit is predictive of progression of damage, as is the degree of damage already accrued[9]. More recently, we have shown that there is a small group of patients who go into remission[10], and this is linked to lower levels of previous disease activity.

Through the database we were also able to determine that patients with PsA were at an increased risk of death, and that while causes of death were similar to those observed in the general population, the increased mortality risk is predicted by disease severity at presentation[11,12]. We have also determined that these patients have a reduced health related quality of life, and that their satisfaction with health is related to features other than the disease process[13]. This longitudinal observational study has also provided information on disease features such as dactylitis and spondylitis, laboratory abnormalities such as hyperuricemia, and drug response.

Past and present studies are combining the clinical information with genetic information. Considerable attention has been given to HLA antigens that occur more frequently among patients with PsA than the general population. Some of these genetic markers also identify patients at higher risk of disease progression and are stronger predictors than clinical features at presentation to the clinic.

ANALYSIS ISSUES

Care is required in the analysis of the data that arise from a longitudinal database. In general, clinical outcomes may be related to many predictor variables, and these predictor variables are often correlated with each other. This contrasts with the situation in a clinical trial, for which, usually, there are a small number of questions linked to treatment; and randomization is used, among other things, to make treatment assignment unrelated to other predictor variables.

With a large number of predictor variables, analysis methods must allow the effect of individual variables to be distinguished. Also, the masking of a real effect or detection of a false effect due to failure to adjust for the importance of another variable, termed confounding, must be considered. The use of regression models that relate an outcome variable to multiple predictor variables is the primary means to achieve these aims.

Outcome variables may take on a variety of forms: Some are dichotomous yes/no variables, such as back involvement in PsA; others are time variables, such as the time to the development of joint damage or the time to death; others are count variables, such as the total number of damaged or the total number of swollen joints. Fortunately, regression models for most types of outcomes have been developed.

One challenging aspect of longitudinal data analysis is to use methods that allow for the correlation between observations of the same variable at different clinic visits for the same patients. Essentially, methods must recognize that information from 2 visits by the same patient is not the same as that obtained from 2 visits by different patients. A second challenge is to make appropriate allowance for the wide variation in the time of clinic entry relative to disease onset and variation in length of followup.

It is not possible here to give a comprehensive survey of methods for the analysis of longitudinal data. However, 2 examples of the use of a particular methodology will be given. In patients with PsA damaged joints develop over time. To chart the condition of a patient at any point in time, states can be defined based on the number of damaged joints. One possibility is to define 4 states defined by no damage, 1–4, 5–9, and 10+ damaged joints. It is then possible to build up a regression model for the rate at which patients move from one state to the next and to study how this rate depends on predictor variables. Note that since damage is irreversible, movement in only one direction is possible. The use of such a model led to characterization of the relationship between damage and

swollen joints, erythrocyte sedimentation rate, sex, and medication[8].

In contrast, if a model is to be developed for quality of life, then the possibility of both improvement and deterioration must be present. For patients in the PsA database for whom information on the Health Assessment Questionnaire (HAQ) is available over time, 3 states can be defined based on HAQ scores of (0–0.49), (0.5–1.5), and (1.51–3). These states are taken to represent no, moderate, and severe disability. In this situation, a model will need to have 2 transition rates between states, one for improvement and one for deterioration. The use of this model, based on the PsA database, leads to the conclusion that patients spend, on average, twice as long in the no-disability state versus the others. Also, over a 10-year period, 46% of patients did not change state, 27% changed in only one direction, and 27% both improved and worsened. The identification of the large fraction of patients in the latter group is important information for the design of clinical trials that involve quality of life measures.

KEEPING PATIENTS INVOLVED

No clinical database can be useful for research purposes unless patients make regular clinic visits and are willing to facilitate the detailed data collection needed. It is to be hoped that patients can recognize that they are partners in the research effort. Thus, while it is true that patients who attend a specialized clinic will usually be receiving care from very knowledgeable physicians and will be eligible for treatments perhaps only available in clinical trials, their participation in important observations should equally be stressed. Means to do this in our PsA clinic include the publication of a patient newsletter, the maintenance of a website reporting the results of studies, and the use of a patient satisfaction questionnaire. Of course, the personal relationship between patient and physician is critical. This relationship is strengthened through ensuring that there is a consistent clinical observer for each patient despite the inevitable turnover in training fellows and similar staff.

To avoid patient loss to followup, there is also the practical need for an appointment procedure that generates a regular schedule of clinic visits, a program to remind patients who are "no-shows" for clinic appointments, and means, such as the identification of other contact persons, to track patients if they are temporarily lost to followup.

CONCLUSION

The PsA clinic at the University of Toronto provides one example of the value of a carefully designed clinical database in undertaking longitudinal cohort studies of important clinical questions in rheumatology. The questions addressed are different from those of clinical trials, but no less important. Funding for clinical databases that can provide high quality data should be an important aspect of any research strategy in rheumatology.

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