Mandatory pharmacosurveillance – A Canadian model for access to therapy and research

S.G. Barr, L. Martin, C. Chung[1], W.P. Maksymowych[1]

Department of Medicine, University of Calgary and [1]Department of Medicine, University of Alberta, Alberta. Canada.

Susan G. Barr, MD, MSc, FRCPC, Assistant Professor; Liam Martin, MB, MRCPI, FRCPC, Associate Professor; Cecilia Chung, MD, Research Fellow; Walter P. Maksymowych, FRCPC, Professor.

Please address correspondence to:
Prof. Walter P. Maksymowych,
562 Heritage Medical Research Building,
University of Alberta, Edmonton,
Alberta, Canada T6G 2S2.
E-mail: walter.maksymowych@ualberta.ca

Clin Exp Rheumatol 2004; 22 (Suppl. 35): S39-S43.

Key words: Rheumatoid arthritis, pharmacovigilance, observational study, biological therapy.

ABSTRACT

Regulatory authorities in Canada have expressed a vital need for pharmacoepidemiological data on long-term effectiveness, safety, and cost-benefit of new therapies, particularly in comparison to currently available therapies, in routine clinical practice to allow informed decision making in listing new therapies on formulary. We describe the evolution of a new model of pharmacosurveillance involving a partnership between academic and community rheumatologists, government, and industry whereby access to therapy is conditional on participation in an industry-funded pharmacosurveillance study that assesses long-term effectiveness, safety, and cost-benefit. Though funded by industry, the program is administered by government and designed and operated at arms length from industry. The clinic data sheets are available at www.altarheum.com. The program also provides a sustainable model for promoting observational research on therapeutics in general.

Introduction

Rheumatic disease management has changed dramatically in recent years, particularly with new strategies of early aggressive treatment to prevent joint damage, and novel therapeutic regimens that include new disease-modifying drugs and biologic response modifiers used alone or in combination. It is anticipated that the need for pharmacoepidemiological studies will increase exponentially in the next decade as rheumatologists will be required to weigh the costs, adverse effects and benefits of a growing number of expensive new therapeutic agents in order to make complex treatment decisions. Furthermore, availability of this information in unselected patient populations will increasingly constitute an essential pre-requisite to regulatory approval in many jurisdictions around the world. The purpose of this paper is to present the development of a unique model of pharmacosurveillance in the Province of Alberta that not only promotes research in this area but also presents a new model for access to and health care delivery of new therapeutic agents.

The existing landscape of pharmacosurveillance

Our understanding of the long-term risks associated with biologic response modifiers in rheumatic diseases has come largely from spontaneous voluntary reporting and clinical trials with open-label follow-up of trial participants. Clinical trials have a limited ability to document safety due to their relatively small sample size, short duration and inclusion of highly selected patients who differ from those treated in usual practice with respect to comorbidities and cointerventions. Spontaneous reporting systems, such as the FDA MedWatch, allow health professionals and consumers to report serious problems that might be drug-related. Such voluntary pharmacovigilance programs are useful for generating alerts regarding possible rare adverse events which then require further study to confirm the association and estimate risk using administrative databases or specialized disease registries or cohorts. Examples of administrative databases include those developed under Medicaid and Health Maintenance Organizations in the USA, Government Health Insurance Plans in Canada, and the General Practice Research Database in the United Kingdom. Administrative claims data arise from a person's use of the health care system and, in some countries, it is possible to link medication use from pharmacy databases with health care utilization data and diagnostic information while respecting

confidentiality (1). Advantages of population-based administrative databases include the ability to conduct studies relatively quickly and inexpensively, the ability to study rare outcomes due to the large sample size, low recall bias, and the ability to calculate incidence rates. However, claims data are not collected for research purposes and this results in problems due to missing data. For example, in-patient drug exposures are often not captured and information on important known confounders is not available. In addition, diagnostic codes may not be valid, leading to difficulty in the meaningful interpretation of data (2).

The best source of data for testing of pharmaco-epidemiological hypotheses are special purpose computerized patient registries and prospective longitudinal observational cohort studies. Since the introduction of biologic response modifiers, registries of patients treated with these agents have been developed in Sweden (3), Spain (4), and the United Kingdom (5). The National Databank for Rheumatic Diseases (NDB) is a large observational cohort study of rheumatic disease outcomes among patients treated with traditional therapies as well as biological agents (www.arthritis-research.org). While most would agree that studies of this type are important, it is often difficult to find a stable source of funding to ensure their long-term success. The existing registries have pieced together support through grants from pharmaceutical companies, research foundations, government and rheumatology societies. An additional major limitation is that these registries have not been administratively organized to ensure that participation is mandatory, raising concerns related to selection bias. While it is generally agreed that the pharmaceutical industry should be responsible for providing post-marketing safety data, it is probably not appropriate for them to collect these data, not only due to perceived conflict of interest and often limited duration of surveillance, but also because many patients will be treated with multiple biologic agents over time which will not be captured by their single agent registries.

Pharmacosurveillance–The Alberta model

The Alberta model involves a unique partnership between government, industry and a group of academic and community rheumatologists known as the RAPPORT (Rheumatoid Arthritis Pharmacovigilance Program and Outcomes Research in Therapeutics) Team. The evolution of our current program and preliminary results are presented below.

The setting

Alberta has a population of just over 3 million with approximately two-thirds residing in the two major centres (Calgary and Edmonton) and the remaining third in rural areas. All rheumatologists practice in the two main centres which each have a University with a medical school. Alberta has a publicly funded and administered health care system that guarantees universal access to medically necessary services. Under the Canada Health Act, the Ministry of Health and Wellness provides Albertans with full coverage for health care and maintains administrative claims databases that document utilization of health care resources. All patients over age 65 receive medications free of charge through Alberta Blue Cross, and others are able to purchase coverage for a nominal fee.

Access to biological therapies for the management of rheumatoid arthritis (RA) in routine clinical practice has proved to be a major challenge for Canadian rheumatologists, as in most other countries. Although a federal agency, the Therapeutics Products Directorate (TPD), conducts a scientific review and grants marketing approval for new therapeutics, individual Canadian provinces also conduct scientific reviews and decide whether new therapeutics should be listed on the Provincial Formulary. This listing is mandatory for reimbursement through provincial health care insurance plans. The introduction of biologic response modifiers has caused considerable difficulty for provincial drug formulary committees due to their lack of familiarity with these agents, the unprecedented costs of these therapies for perceived non-life threatening illnesses and the outcry from patient organizations for immediate access to them. Though many provinces had undertaken to evaluate comparative effectiveness and cost-effectiveness as the basis for decision making, a recent survey of key provincial formulary consultants across Canada highlighted the lack of availability of such data (6). An impressive finding of the survey was the consistency of the data requirements for the evaluation process: long-term effectiveness and safety in comparison to an active comparator, cost-effectiveness, and impact on overall health care costs to the province. Only one province reported having criteria for determining whether a drug is cost-effective and no province reported that listing a drug was ever conditional on a cost-effectiveness study being conducted during its use in routine clinical practice. The needs of provincial formularies are not dissimilar to those previously cited by other regulatory agencies and their advisory committees (e.g. the National Institute for Clinical Excellence) (7).

Implementation of the Pharmacosurveillance Program – Phase I

Prior to approval of biologic agents in Alberta in 2003, patients failing traditional disease-modifying antirheumatic drugs (DMARDs) were able to receive infliximab from 2000 onwards through a Special Access Program funded by Schering Canada. Consecutive patients commencing therapy with infliximab for a clinical diagnosis of RA gave consent to allow data collection. The Program was based at the two academic centres, although patients were referred by both community- and University-based rheumatologists for supervision of infusions and data collection. Infliximab was given according to the standard dosing schedule of 3 mg/kg IV at weeks 0, 2, 6 and every 8 weeks thereafter. Dose adjustments and co-interventions were allowed according to standard practice at the discretion of the primary rheumatologist. At the Edmonton site, data was also collected by the academic rheumatologists on consecutive patients starting either etanercept (25 mg SC twice weekly) or leflu-

nomide (20 mg PO daily) as a comparator group. This approach represents a new-user design (analogous to an inception cohort) in order to avoid the biases that can occur with the inclusion of prevalent drug users, such as the underestimation of adverse events that occur early in the course of therapy and adherence bias. Data collection was not mandatory under the Special Access Program, although both centres collected data on a voluntary basis for all patients, including basic demographics, disease duration and DMARD history. Outcome variables included tender and swollen joint counts, visual analogue scales for pain and global health assessed by the patient and physician, the Health Assessment Questionnaire or ClinHAQ, acute-phase reactants, and x-rays. Health-related quality of life was measured using the Medical Outcomes Short Form 36 item questionnaire (SF-36) and EuroQol. Adverse events and co-medications were updated and laboratory monitoring was performed according to usual clinical practice. Data was collected at baseline, week 14 and every 6 months thereafter, or more frequently if clinically indicated. Upon drug discontinuation, the date of the last dose and primary reason for stopping were recorded.

Implementation of Pharmacosurveillance Program – Phase II

A unique approach to the use of new therapeutics was undertaken in Alberta to address the data needs of the provincial drug formulary whilst ensuring access to therapy without incurring cost to the taxpayer related to the process of data collection. Formulary listing for both infliximab and etanercept was granted by Alberta Health on April 1, 2003 and was conditional on two key requirements: 1. A province-wide pharmacosurveillance study funded by industry; 2. Mandatory participation in the pharmacosurveillance study by patients and their rheumatologists. In addition, use of biologic agents is restricted to RA patients who have failed methotrexate, methotrexate combined with another DMARD, and leflunomide. Mandatory participation is administratively organized by asking patients to sign a consent form that is part of the provincial access-to-therapy form and by having rheumatologists sign the same form indicating that they will participate in the study. Furthermore, continuing provision of the therapeutic agent is conditional on the rheumatologist providing data proving that certain pre-specified efficacy outcomes have been met. These include an ACR20 or a DAS response, and a HAQ improvement of ≥ 0.22 after 12 weeks of therapy. Maintenance of this response must be documented every 6 months thereafter. It was possible to convince Alberta Health of the feasibility of this approach because pharmacosurveillance of RA patients on biologics had become the norm in routine clinical practice during the period of the Special Access Program for infliximab. Since formulary listing, the majority (> 90%) of patients treated with infliximab and etanercept have had the cost of the drug covered by the provincial health care insurance plan through Alberta Blue Cross with the remainder accessing the drug via private insurance plans. Those on private insurance plans were strongly encouraged to participate as Alberta Blue Cross indicated that the same data would be required from such patients should they ever switch to the government plan.

The design of the pharmacosurveillance study was finalized after a comprehensive review of existing international registries for biologics in RA (UK, Germany, Sweden), a review of the NDB database , and incorporation of OMERACT recommendations for the conduct of longitudinal observational studies (8, 9). In addition, recommendations were obtained from a retreat attended by representatives from industry, government and members of the study scientific committee composed of academic and community-based rheumatologists as well as invited external experts on the epidemiology and health economics of rheumatic diseases.

A data collection form has been developed which includes the demographic, disease activity, quality of life and laboratory variables described above for Phase I of the study, as well as some additional instruments. The CLINHAQ was chosen in view of its sensitivity to change over the MDHAQ, although those questions in the MDHAQ not included in the CLINHAQ have been incorporated into our questionnaire to allow comparability with longitudinal cohorts internationally (11, 12). In addition, co-morbidities are ascertained using a validated questionnaire (10). Resource use and illness-related employment history components of the questionnaire were developed with input from the Alberta Institute of Health Economics which is represented on the scientific committee. The resource utilization questionnaire captures use of inpatient and outpatient services, including visits to physicians and allied health professionals, diagnostic tests, surgical procedures, and medications. Adverse events are documented according to the most recent recommendations of the OMERACT working group on toxicity (www.ilar.org). In addition to a descriptive record of the adverse event, the event is classified according to system involvement, severity, causality, and outcome. Withdrawals are documented, as well as the reasons for withdrawal. Patients who withdraw continue to be followed at 6-monthly intervals. The program is administered by clinician nurses trained in joint examination techniques who provide real time feedback to the primary rheumatologist regarding patient outcomes. The entire data collection form is now available on our website (www.altarheum.com). We are currently merging data from the two sites into a province-wide population-based dataset that will include RA patients starting therapy with biologic agents and as well as a comparator group of patients starting new or traditional DMARDs. Data ownership belongs to the RAPPORT Team.

Preliminary results

The following preliminary results from our program are presented as an example of pharmacosurveillance data demonstrating the relative safety and effectiveness of RA therapeutic agents in us-

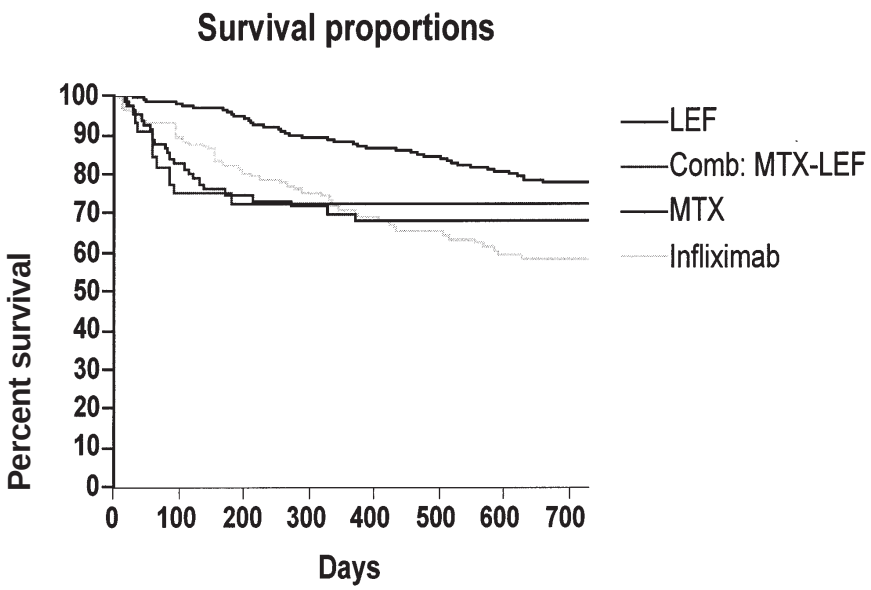

Fig. 1. Drug survival curves for patients treated with leflunomide, combination leflunomide and methotrexate, methotrexate, and infliximab.

ual clinical practice. Comparative treatment survival was assessed among new users of leflunomide (N = 81), methotrexate (7.5 to 37.5 mg/week; N = 250), combination leflunomide plus methotrexate (N = 44) or infliximab (N = 163) followed for 2 years in routine clinical practice at the Edmonton site. Data for the methotrexate group was obtained by chart review of patients followed at a specialized RA Clinic between 1985 and 1994.

The mean age of the patients was 56 years and 69% were females. As expected, the methotrexate group had a shorter mean disease duration (7 years) compared to that of the other three groups (16 years) and had tried a smaller mean number of DMARDs prior to study entry (0.24 versus 3). During a 2-year follow-up, 30% on leflunomide, 19% on methotrexate, 27% on combination leflunomide plus methotrexate, and 33% on infliximab had discontinued initial therapy (Fig. 1). Lack of efficacy was the reason for stopping therapy among 15% on leflunomide, 5% on methotrexate, 9% on combination leflunomide plus methotrexate and 18% on infliximab, with adverse events being responsible for the remaining drop outs. These results are concordant with those reported in controlled clinical trials (13, 14). Kaplan-Meier analysis showed that patients on infliximab had a higher proportion of drug survival than patients on leflunomide or the combination of leflunomide/methotrexate in the first six months. This difference became progressively less apparent over time and by two years both leflunomide and combination leflunomide plus methotrexate had better survival than infliximab. These results suggest that early side effects and lack of efficacy result in discontinuation of leflunomide or the combination of leflunomide plus methotrexate, but these regimens appear to maintain effectiveness and tolerability over time among those who "survive" the initial treatment period. In contrast, there was a steady withdrawal of patients on infliximab over 2 years primarily due to infusion reactions and loss of efficacy.

Survival on leflunomide was reported as being somewhat worse in several recent studies that included analyses of both prospective observational cohorts as well as administrative databases (15-17). One explanation for these differences could be that leflunomide became available in Alberta 3 years prior to biologics. Consequently, patients on leflunomide had few alternative therapeutic options available to them until recently. In addition, one study reported that patients receiving leflunomide tend to be older, have more severe structural damage, and have lower inflammatory activity (16). It seems possible that, where access to all treatment options is available, confounding by indication bias may result in biologics being preferentially administered to patients with more active inflammatory disease.

Conclusions

The RAPPORT team initiative represents a unique collaborative effort between community and academic rheumatologists, industry and the government to permit pharmacoepidemiologic research on the relative costs and benefits of current and future biological agents as well as comparator disease modifying drugs in everyday rheumatological practice. A unique advantage of our cohort relates to the fact that our government has made data collection mandatory in order for patients to access biological agents through the provincial drug insurance plan. As a result, we anticipate collecting population-based data on the safety and benefits of these agents for the entire province of Alberta. Future economic analyses will be possible by linking our data to the Alberta administrative claims databases that document utilization of health care resources for all Albertans under our publicly funded universal health care system. Additional strengths of our study include its prospective, new-user design as well as its sustainability through the collaborative partnerships described. We believe that academia can play a pivotal role in pharmacovigilance as a trusted third party with clinical and research expertise that is independent of industry and government.

References

1. VERSTRAETEN T, DESTEFANO F, CHEN RT, MILLER E: Vaccine safety surveillance using large linked databases: opportunities, hazards and proposed guidelines. *Expert Review of Vaccines* 2003; 2: 21-9.
2. CRONK CE, MALLOY ME, PELECH AN *et al.*: Completeness of state administrative databases for surveillance of congenital heart disease. *Birth Defects Res* 2003; 67: 597-603.
3. VAN VOLLENHOVEN RF, ERNESTAM S, HARJU A, BRATT J, KLARESKOG L: Etanercept versus etanercept plus methotrexate: a registry-based study suggesting that the combination is clinically more efficacious. *Arthritis Res Therapy* 2003; 5: R347-51.
4. GOMEZ-REINO JJ, CARMONA L, VALVERDE VR, MOLA EM, MONTERO MD and the BIO-

BADASER GROUP: Treatment of rheumatoid arthritis with tumor necrosis factor inhibitors may predispose to significant increase in tuberculosis risk: a multicenter active-surveillance report. *Arthritis Rheum* 2003; 48: 2122-7.

5. SILMAN A, SYMMONS D, SCOTT DG, GRIFFITHS I: British Society for Rheumatology Biologics Register. *Ann Rheum Dis* 2003; 62 (Suppl. 2): 28-9.
6. WEST R, BORDEN EK, COLLER JP, RAWSON NSB, TONKS RS: "Cost-effectiveness" estimates result in flawed decision-making in listing drugs for reimbursement. *Can J Pub Health* 2002; 93: 421-5.
7. NATIONAL INSTITUTE FOR CLINICAL EXCELLENCE: Guidance for the use of etanercept and infliximab for the treatment of rheumatoid arthritis. 2002: *Technology Appraisal Guidance No. 36* [www.nice.org.uk].
8. WOLFE F, LASSERE M, VAN DER HEIJDE D *et al*.: Preliminary core set of domains and reporting requirements for longitudinal observational studies in rheumatology. *J Rheumatol* 1999; 26: 484-9.
9. SILMAN A, SYMMONS D: Reporting requirements for longitudinal observational studies in rheumatology. *J Rheumatol* 1999; 26: 481-3.
10. SANGHA O, STUCKI G, LIANG MH, FOSSEL AH, KATZ JN: The self-administered comorbidity questionnaire: A new method to assess comorbidity for clinical and health services research. *Arthritis Rheum* 2003; 49: 156-63.
11. WOLFE F: Which HAQ is best ? A comparison of the HAQ, MHAQ, and RA-HAQ, and a rescored 20 item HAQ (HAQ20): analyses in 2491 rheumatoid arthritis patients following leflunomide initiation. *J Rheumatol* 2001; 28: 982-9.
12. PINCUS T, SWEARINGEN C, WOLFE F: Toward a multidimensional Health Assessment Questionnaire (MDHAQ): assessment of advanced activities of daily living and psychological status in the patient-friendly health assessment questionnaire format. *Arthritis Rheum* 1999; 42: 2220-30.
13. SMOLEN JS, KALDEN JR, SCOTT DL *et al*.: Efficacy and safety of leflunomide compared to placebo and sulfasalazine in active rheumatoid arthritis: a double blind randomized, multimember trial. *Lancet* 1999; 353: 259-66.
14. EMERY P, BREEDVELD FC, LEMELL EM *et al*.: A comparison of the efficacy and safety of leflunomide and methotrexate for the treatment of rheumatoid arthritis. *Rheumatology* 2000; 39: 1-11.
15. SIVA C, EISEN SA, SHEPHERD R *et al*.: Leflunomide use during the first 33 months after food and drug administration approval: experience with a national cohort of 3,325 patients. *Arthritis Rheum* 2003; 15;49: 745-51.
16. GEBOREK P, CRNKIC M, PETERSSON IF, SAXNE T: Etanercept, infliximab, and leflunomide in established rheumatoid arthritis: clinical experience using a structured follow up programme in southern Sweden. *Ann Rheum Dis* 2002; 61: 793-8.
17. VAN ROON EN, JANSEN TL, MOURAD L *et al*.: Leflunomide in active rheumatoid arthritis: a prospective study in daily practice. *Brit J Clin Pharmacology* 2004; 57: 790-7.