Editorial

Power of the Database: An International Approach to Studying Longterm Rheumatoid Arthritis Therapy

A 45-year-old teacher with a 10-month history of rheumatoid arthritis (RA) initially responding to methotrexate (MTX, 25 mg/wk) has relapsed with increasing pain, swelling, and functional limitation. Examination shows synovitis of the wrists, knees, and small joints of the hands and feet, and the C-reactive protein and erythrocyte sedimentation rate are elevated. Faced with this scenario, many rheumatologists would escalate antirheumatic therapy. Several options are considered, including new agents with clinical trial data showing remarkable clinical responses and radiographic protection. However, both her parents died from cancer several years ago, and she is somewhat wary about the potential longterm risks of treatment of her arthritis. She will agree to whatever you recommend, but has heard that the treatment may cause cancer and wants to know her longterm risk. Do we know her risks? What would we give her by way of evidence? What can we tell her about the risk for MTX, an agent in use for more than 20 years? Will there be answers with more confidence in another 10 years? What about these other agents?

This vignette epitomizes a major problem in RA management: rare, longterm serious toxicity that may be treatment-related. This issue was common to all treatments with traditional agents such as injectable gold[1] and D-penicillamine[2], and similar issues have now arisen with the newer tumor necrosis factor (TNF) agents[3]. Late-appearing malignancies and unusual serious infections are well known examples, but there are numerous others unified by their unpredictable nature. The example of lymphoproliferative disease and immunosuppressive therapy is apt: even repeated efforts over the years to clarify the relationship[4-12] have not settled this issue.

We briefly review drug surveillance and the study of drug toxicity including the example of azathioprine and lymphoid malignancy in RA. The problem, our limited knowledge of longterm drug attribution, arises from many factors including the variable nature of the disease itself and the variable response to treatment. In addition, no study has been of satisfactory design and or sufficient size to adequately address this problem. One solution is an international collaborative project on database study design and implementation. Its purpose is to construct a sizeable, longterm, composite database. It is an ambitious project designed to overcome limitations of single databases and with time yield more valid and quantitative evidence to inform patient discussions like that described above. Because such information is clearly in the best interest of patients, we argue that clinicians have a responsibility to pursue it.

GENERAL ASSESSMENT OF DRUG TOXICITY

With the major growth in the 1950s and 1960s in pharmaceuticals and their formal regulation, numerous adverse event reporting systems were established. These systems were generally voluntary, and although they remain useful in signal detection, even the statisticians who designed them[13] recognized their limitations. In particular, voluntary systems have no reliable measure of those with a given adverse reaction or of those exposed and so at risk for it. Both numerator and denominator are unreliable. Additionally, none of the systems has a persuasive control group. Even contemporary analyses with these systems, such as the recent US Food and Drug Administration update on TNF usage and lymphoma[14], entail selection bias regarding participation, case ascertainment, lack of concurrent controls, and information on important covariates. In the 1970s and 1980s, pharmacoepidemiology broadened to include record-linked drug monitoring systems, administrative databases adapted to clinical questions of drug toxicity, and large computerized general medical databases such as the UK General Practice Research Database[15]. However, these databases also have limitations, especially regarding diagnosis misclassification and inadequate confounder information such as drug exposures[16], and none has been adequate for use in RA.

DRUG TOXICITY IN RA; THE CASE OF AZATHIOPRINE

In the 1970s and 1980s a number of studies[4-7] were done to estimate the increased risk of lymphoproliferative malignancy due to RA alone, and the additional risk due to azathioprine use. Two of these with strong designs[6,7] found similar estimates for lymphoproliferative disease in the background populations (2.0 cases per 1000 for both studies), and in RA patients treated with azathioprine (8.0 cases per 1000, 95% confidence interval, CI: 3.7, 15.2; and 7.5 cases per 1000, 95% CI 1.4, 18.5). Only one of these[7] (with controls matched for disease duration, age, sex, seropositivity, and azathioprine exposure) was able to separately estimate a rate due to RA alone, compared to the normal population: 4.8 cases per 1000, 95% CI 0.4, 13.8 (Silman A, personal correspondence, 1990). A subsequent study[17] has also confirmed that disease activity itself is a significant risk factor. Finally, a 5-year prospective study in

1200 RA patients taking azathioprine, even though powered to detect a 3-fold increase in cases over controls, had too few cases to permit multivariate analysis[8].

The reasons for the limitations of these studies are many. RA is highly variable and compounded by polypharmacy, both current and past. The absence of clear, widely applicable prognostic factors makes RA study populations inevitably more heterogeneous. Adequate information on confounders for analysis of longterm observational studies is difficult at best, and in RA it is compounded by the difficulty of measuring disease severity and capturing the relevant drug exposure information. Furthermore, epidemiology itself has limitations. Historically, the accuracy of results of case-control designs, even if prospectively planned, has not been satisfactory[18,19]. On the other hand, longterm cohort studies are expensive and time consuming and require careful attention to design if the suspected effect size is not large. A positive observational study reporting a small effect (such as a doubling of risk) may be viewed skeptically and called hypothesis-generating. In general, critics have argued that the focal power of epidemiology is limited and rarely able to discern small effects in an unbiased manner[20]. More recently, inception cohorts have been established in RA[21-26] (Bijlsma H, personal communication, 2004; Voskuyl A, personal communication, 2004) that should help avoid major selection bias and so permit more accurate assessment of RA prognosis. In addition many countries have established, or are in the process of establishing, nationwide registries for patients starting TNF-α therapy.

However, as the azathioprine experience shows, it is difficult to adequately design single studies large enough to give definitive answers about rare, delayed toxicity, and it is unlikely that any single inception cohort will have enough patients with severe disease to be able to address these hypotheses.

All this has conspired to make studies of drug attribution in RA difficult. At the same time reports of longterm increased morbidity and mortality[27,28] in RA appeared. To compound these difficulties, most new agents for RA developed since 1990 have had smaller, not larger, safety databases at initial marketing because targeting biologic markers rapidly suppresses inflammation so that efficacy can be demonstrated in smaller and shorter trials. However, this leads to a corresponding loss in the ability to discern longterm rare adverse events.

THE INTERNATIONAL RHEUMATOID ARTHRITIS DATABASE (IRAD)

To help acquire better longterm evidence on drug toxicity, the IRAD initiative was established. It consists of 2 projects: (1) a collaboration of current and future RA databases and creation of a composite, representative database (IRAD Databank); and (2) a research agenda to test the validity and extent of pooling among RA databases. The genesis of IRAD involved academic, pharmaceutical, and regulatory scientists under the auspices of OMERACT (an informal international entity for professionals interested in outcome measurement in rheumatology) in the 1990s and they published a preliminary proposal for a longterm monitoring program in 2000[29]. Subsequently 2 large expert meetings were held to discuss need and feasibility. We were involved from the outset and have now drawn up the fundamental design for the implementation of IRAD that is outlined below. The project is already informally facilitating collaboration among existing and newly establishing RA databases and is now being implemented as a website repository (www.iradproject.com [cited May 3, 2004]) for information on the design and operations of current and future RA databases. As IRAD becomes operational it will be a web-based project with participating centers having equal access. Several new national databases, often mandated by reimbursement authorities, have been established subsequent to the recent introduction of the biologic agents. Finally, since there is no precedent to an undertaking of this type in a chronic disease, IRAD should become a pilot for similar initiatives that may be considered in the future for other chronic diseases.

IRAD FUNCTIONS

Repository of RA databases. IRAD serves an umbrella function as a repository on design and operation of RA databases worldwide. It is proactive in understanding and implementing the parallelisms in design and operations that likely will be needed for future pooling. It will also coordinate, advise, and aid in initiating new RA databases. The website will maintain a comprehensive and transparent inventory of (1) various database designs and operations, and (2) differing confidentiality, privacy, and ethics considerations relevant to databases across countries. Informal yearly meetings will review the design and operation of existing and planned databases and the findings of the research agenda as they unfold. Databases for a variety of purposes are now emerging, some public, some proprietary, including a growing collection of national registries of TNF usage[30]. All have been invited to participate in IRAD and almost all have responded positively.

IRAD Databank. IRAD will physically house a composite database called the IRAD Databank. It will consist of yearly contributions from participating databases. Specifically, these will be 10% random samples of the past year's database registrants. IRAD Databank thus will enlarge over time. Each year a new random subset will be contributed, along with followup data on registrants from previous years' subsets. The use of a randomized design will make the core database more representative than any single database or group of databases, and its use for hypothesis-testing with nested case-control designs and for descriptive purposes will thus be enhanced. Further, it will primarily draw on existing international resources. In return for participation, all centers will have unrestricted use of IRAD data, so there will be mutual benefits. The bidirectional relationships between participating databases and IRAD and its Databank are illustrated in Figure 1. The IRAD Databank will then be available for research questions informed by IRAD's research agenda. Past empirical work will be used as a preliminary guide regarding minimal design criteria, core set of domains, and reporting requirements for longitudinal observational studies in RA[31,32].

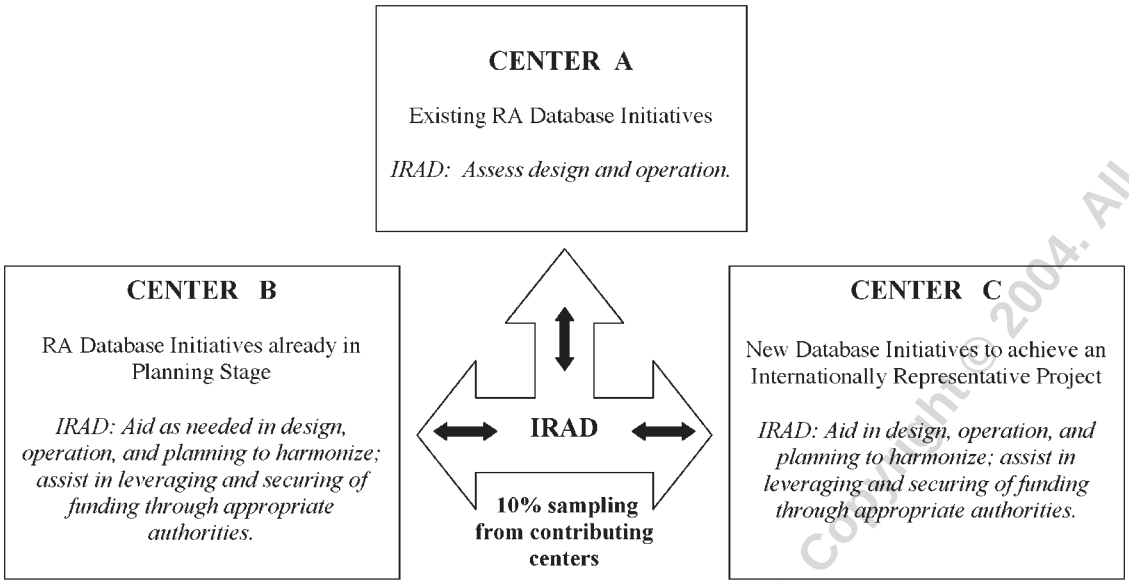

Figure 1. IRAD structure and operations.

Research facility for participants. In return for database participation and the contributed information from the 10% random samples each year, databases will have the right to unrestricted use of the IRAD Databank or any portion of it. It is hoped that this will serve generally as a research incentive.

Data pooling research agenda. Establishing a research agenda on database pooling is a logical step in the growth of evidence-based medicine in rheumatology. Pooling across randomized trials and observational studies has been widely done in other areas in medicine[33]. In selected areas such as blood pressure or blood lipids, pooling is accomplished with existing metaanalysis methodology[34-36], even though issues of heterogeneity often remain[37]. In general, the more design parallelism seen in the component studies, the less controversial is their pooling. The extreme of this methodology is an identical design throughout, i.e., a multicenter trial with a common protocol, whose analysis is readily accepted.

IRAD proposes to test existing databases to experimentally establish when pooling is justified. The first step is attaining transparency regarding structure and operations of existing RA databases, which now number at least 20. Secondly, IRAD will test the participating databases by asking each to analyze a fixed battery of questions. This will allow indirect assessment of the data quality. It is likely that participation will mean a database fulfills certain minimal design and reporting criteria[31,32]. The results can then be compared for patterns that may relate to the varying database structure and operations. Currently, there is virtually no information on database poolability. Existing RA database personnel have expressed a willingness to participate.

Exploration of new toxicity questions. When the IRAD Databank is sufficiently large, it will be an invaluable resource to explore new queries that will arise regarding possible drug toxicity. The investigations will use longitudinal cohorts housed in the IRAD Databank and be augmented with nested case-control protocols as needed, tailored to the question of interest.

Resource to industry. There will be a proviso for subscriber use of the data for pharmaceutical firms that help support the project. This will make the Databank more generally available for research purposes. For example, it should be useful in estimates of control event rates in samples free of many of the selection and other biases that confound most pharmaceutical data.

The current rapidly expanding RA armamentarium makes IRAD a timely proposal. The numerous national databases being constructed, plus ongoing databases, will all be adjunctive in this effort. Its strength lies in its design, particularly its prospective core dataset common to all databases and its yearly contributions of random subsets. An international database is in the best interest of patients. As clinicians we have a responsibility to implement it.

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Note: OMERACT stands for "Outcome Measures in Rheumatology," an informal entity for professionals interested in outcome measurement in rheumatology. OMERACT is chaired by an international committee (Peter Tugwell, Maarten Boers, Peter Brooks, Vibeke Strand, and Lee Simon) endorsed by the International League for Rheumatology, and has held conferences under the auspices

of the World Health Organization beginning in 1992 in The Netherlands. In conjunction with the ILAR, OMERACT has had a working group on Drug Toxicity and Safety since 1994, led by Peter Brooks and Richard Day. Its focus was to develop a toxicity index for use in all rheumatology clinical trials, and to find a way forward to better record longterm RA outcomes, especially regarding drug toxicity[38,39].

REFERENCES

1. Jones G, Brooks PM. Injectable gold compounds: an overview. Br J Rheumatol 1996;35:1154-8.
2. Munro R, Capell HA. Penicillamine. Br J Rheumatol 1997;36:104-9.
3. Shanahan JC, St. Clare W. Tumor necrosis factor-alpha blockage: a novel therapy for rheumatic disease. Clin Immunol 2002;103:231-42.
4. Isomaki HA, Hakuline T, Joutsenlahti U. Excess risk of lymphoma, leukemia and myeloma in patients with rheumatoid arthritis. J Chron Dis 1978;31:691-6.
5. Katusic S, Beard CM, Kurland LT, Weis JW, Bergstralh E. Occurrence of malignant neoplasms in the Rochester, Minnesota, Rheumatoid Arthritis Cohort. Am J Med 1985;78 Suppl 1A:50-5.
6. Prior P. Cancer and rheumatoid arthritis: Epidemiologic considerations. Am J Med 1985;78 Suppl 1A:15-21.
7. Silman AJ, Petrie J, Hazelman G, Evans SJW. Lymphoproliferative cancer and other malignancy in patients with rheumatoid arthritis treated with azathioprine: a 20 year follow up study. Ann Rheum Dis 1988;47:988-92.
8. Hickey AR, Urowitz MB, et al. The rheumatoid arthritis azathioprine registry: An update. In: Rainsford KD, editor. Advances in anti-rheumatic therapy. Boca Raton: CRC Press; 1996.
9. Mellemkjaer L, Linet MS, Gridley G, Frisch M, Moller H, Olsen JH. Rheumatoid arthritis and cancer risk. Eur J Cancer 1996;32A:1753-7.
10. Gridley G, McLaughlin JK, Ekbom A, et al. Incidence of cancer among patients with rheumatoid arthritis. J Natl Cancer Inst 1993;85:307-11.
11. Cibere J, Sibley J, Haga M. Rheumatoid arthritis and the risk of malignancy. Arthritis Rheum 1997;40:1580-6.
12. Kremer J. Is methotrexate oncogenic in patients with rheumatoid arthritis? [editorial]. Semin Arthritis Rheum 1997;26:785-7.
13. Finney DJ. Statistical logic in the monitoring of reactions to therapeutic drugs. Methods Inf Med 1971;10:237-45.
14. FDA website [Internet]. CDER Arthritis Advisory Committee Meeting, March 4, 2003 [cited May 2, 2004]. Available from: http://www.fda.gov/oc/advisory/accalendar/cder12532dd03040503.html
15. Garcia Rodriguez LA, Perez Gutthann S. Use of the UK General Practice Research Database for pharmacoepidemiology. Br J Clin Pharmacol 1998;45:419-25.
16. Jick H. Use of automated databases to study drug effects after marketing. Pharmacotherapy 1985;5:278-9.
17. Baecklund E, Ekbom A, Sparen P, Feltelius N, Klareskog L. Disease activity and risk of lymphoma in patients with rheumatoid arthritis: nested case-control study. BMJ 1998;317:180-1.
18. Hurwitz RI, Feinstein AR. Methodologic standards and contradictory results in case-control research. Am J Med 1979;66:556-64.
19. Taubes G. Epidemiology faces its limits. Science 1995;269:164-9.
20. Shapiro S. Point/counterpoint: meta-analysis of observational studies: meta-analysis/shmeta-analysis. Am J Epidemiol 1994;140:771-7.
21. Brennan P, Harrison B, Barrett E, et al. A simple algorithm to predict the development of radiological erosions in patients with early rheumatoid arthritis: prospective cohort study. BMJ 1996;313:471-6.
22. Smedstad L, Moum T, Guillemin F, et al. Correlates of functional disability in early rheumatoid arthritis: study of 706 patients in four European countries. Br J Rheumatol 1996;35:746-51.
23. Gough A, Young A, Bacon P. Objectives and outcome of running an early inflammatory arthritis clinic. Baillieres Clin Rheumatol 1992;6:261-83.
24. Kroot EJ, van Leeuwen MA, van Rijswijk MH, et al. No increased mortality in patients with rheumatoid arthritis: up to 10 years of follow up from disease onset. Ann Rheum Dis 2000;59:954-8.
25. Zeidler H, Merkesdal S, Hulsemann JL. Early rheumatoid arthritis in Germany. Clin Exp Rheumatol 2003;21 Suppl 31:S106-12.
26. Stolt P, Bengtsson C, Nordmark B, et al. Quantification of the influence of cigarette smoking on rheumatoid arthritis: results from a population based case-control study, using incident cases. Ann Rheum Dis 2003;62:835-41.
27. Mitchell DM, Spitz P, Young D, et al. Survival, prognosis, and causes of death in rheumatoid arthritis. Arthritis Rheum 1986;29:706-14.
28. Scott DL, Coulton B, Symmons D, Popert AJ. Long-term outcome of treating rheumatoid arthritis: results after 20 years. Lancet 1987;1:1108-11.
29. Lipani JA, Strand C, Woodworth T, et al. A proposal for developing a large patient population cohort for longterm safety monitoring in rheumatoid arthritis [editorial]. J Rheumatol 2000;27:827-30.
30. Silman A, Klareskog L, Breedveld F, et al. Proposal to establish a register for the long term surveillance of adverse events in patients with rheumatic diseases exposed to biological agents: the EULAR surveillance register for biological compounds. Ann Rheum Dis 2000;59:419-20.
31. 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.
32. Silman A, Symmons D. Minimum reporting requirements for longitudinal observational studies in rheumatology. J Rheumatol 1999;26:481-3.
33. MRC/Cancer Research UK/BHF Clinical Trial Service Unit & Epidemiological Studies Unit [Internet]. [cited May 2, 2004] Available from http://www.ctsu.ox.ac.uk/
34. MacMahon S, Peto R, Cutler J, et al. Blood pressure, stroke, and coronary disease. Part 1. Prolonged differences in blood pressure: prospective observational studies corrected for the regression dilution bias. Lancet 1990;335:765-74.
35. Law MR, Wald NJ, Thompson SG. By how much and how quickly does reduction in serum cholesterol concentration lower risk of ischaemic heart disease? BMJ 1994;308:367-72.
36. Anonymous. Collaborative overview (meta-analysis) of prospective observational studies of the associations of usual blood pressure and usual cholesterol levels with common causes of death: protocol for the second cycle of the Prospective Studies Collaboration. J Cardiovasc Risk 1999;6:315-20.
37. Thompson SG. Why and how sources of heterogeneity should be investigated. In: Egger M, Smith GD, Altman DG, editors. Systematic reviews in health care: meta-analysis in context. 2nd ed. London: BMJ Publishing Group; 2001:157-75.
38. Brooks PM, Day RO. Toxicity of antirheumatic drugs: workshop report. J Rheumatol 1995;22:998-9.
39. Gazarian M, Tugwell P, Boers M, et al. Patient based methods for assessing adverse events in clinical trials in rheumatology. Progress report for the OMERACT drug toxicity working party. J Rheumatol 1999;26:207-9.