A Proposal for Developing a Large Patient Population Cohort for Longterm Safety Monitoring in Rheumatoid Arthritis

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ABSTRACT. This paper proposes the creation of an objectively acquired reference database to more accurately characterize the incidence and longterm risk of relatively infrequent, but serious, adverse events. Such a database would be maintained longitudinally to provide for ongoing comparison with new rheumatologic drug safety databases collecting the occurrences and treatments of rare events. We propose the establishment of product-specific registries to prospectively follow a cohort of patients with rheumatoid arthritis (RA) who receive newly approved therapies. In addition, a database is required of a much larger cohort of RA patients treated with multiple second line agents of sufficient size to enable case-controlled determinations of the relative incidence of rare but serious events in the treated (registry) versus the larger disease population. The number of patients necessary for agent-specific registries and a larger patient population adequate to supply a matched case-control cohort will depend upon estimates of the detectability of an increased incidence over background. We suggest a system to carry out this proposal that will involve an umbrella organization, responsible for establishment of this large patient cohort, envisioned to be drawn from around the world. (J Rheumatol 2001;28:1170–3)

Key Indexing Terms:

DATABASE	SURVEILLANCE	REGISTRY
ADVERSE EFFECTS	TOXICITY	SAFETY

INTRODUCTION

Many of the new products under development for the treatment of rheumatoid arthritis (RA) and other rheumatic diseases may be associated with safety issues related to their pharmacodynamic effects. There may be longterm consequences, which include potential immunosuppression with associated opportunistic infections, new autoimmune conditions, and the development of lymphoproliferative (LP) disorders. Neither preclinical toxicologic studies nor short term clinical trials have, so far, adequately addressed these issues. Even recommendations presented in the International Consensus on Harmonization Guideline on the extent of population exposure for drugs intended for longterm treatment of non-life threatening conditions[1] may not include sufficiently large populations to identify these relatively rare events. We propose the creation of an objectively acquired reference database. Such a database would be maintained longitudinally to provide for ongoing comparison with new rheumatologic drug safety databases collecting the occurrences and treatments of these rare events.

In other patient populations, clinical evidence of serious immunosuppression has correlated with development of these adverse events, but no biologic marker has reliably predicted their occurrence. Although the known association of immunosuppression and adverse events in transplantation patients, for example, closely parallels the degree of immunosuppression resulting from conditioning and antirejection therapies, together with Epstein-Barr virus infection, the causes for an apparent increased incidence of LP disorders in patients with RA are less clear[2].

Based in part on the known association of Sjögren's syndrome with lymphoma in men with Felty's syndrome, it has been presumed that the incidence of LP disease in RA is increased[3,4]. Previous efforts aimed at determining its true incidence following treatment with potential immunosuppressive agents have not been conclusive. For example, data

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The views expressed in this paper are those of the authors and the OMERACT Drug Safety Working Party.

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derived from prospective followup of cohorts (or registries) of patients with RA treated with azathioprine (AZA) have been limited by insufficient size to accurately identify risk, retrospective identification of the population, and/or inadequate size of the control population to account for multiple risk factors[5,6].

It appears that LP disorders may occur more frequently in RA than in the general population. A 3- to 8-fold increase in patients with moderate/severe disease has been estimated[7], with additional increments in those treated with AZA[8-11], and possibly cyclosporin A (CsA)[12-14]. However, longterm followup of the large epidemiologic cohorts necessary to confirm these associations is lacking in most databases. None has been dedicated to the mechanistically based biologic agents recently released.

The clinical picture with methotrexate (MTX) with regard to these events is even less clear. Although an increasing number of reports of LP disorders associated with MTX use in RA are appearing in the literature, the number of cases approximates 50[15] individuals of a total treated population estimated (conservatively) to be 500,000[16], an estimated overall incidence of 0.0001. Such a low incidence (less than the estimates for AZA or CsA), although suggestive, requires confirmation. Disease cofactors are suggested when contrasted with the much lower incidence of LP disease reported with MTX treatment of psoriasis[17] and given the apparent absence of this effect in women treated for trophoblastic tumors[18], identification of events that may contribute to this association become even more challenging.

It is important to consider this retrospective assessment in relation to reports of LP disease in patients with RA receiving many of the recently studied biologic agents: 2 cases of non-Hodgkin's lymphoma (NHL) and one Hodgkin's lymphoma (HL) occurred following relatively short term administration of anti-tumor necrosis factor-α monoclonal antibodies (Mab) to an estimated 150 patients[19,20]; 2 cases of NHL were observed after CAMPATH-1H (anti-CHD 52) Mab administration to 140 patients[21]; and one case was noted after treatment of an estimated 200 patients with a primatized anti-CD4 Mab (Lipani J, personal communication). Should these cases be ascribed to the experimental biologic therapy, previous treatment with potentially immunosuppressive agents in a typically treatment refractory RA patient population, and/or both, or to other factors?

This issue becomes even more important as we begin to identify promising biologic and small molecular agents that are expanding our therapeutic armamentarium in important ways. Based on their hypothesized, or identified, mechanism of action, these treatments may be immunosuppressive. Further, many of the discussions relevant to the use of MTX will be applicable to these experimental products, as the 2 agents will likely be utilized in combination.

PROPOSAL

To more accurately characterize the incidence and longterm risk of these relatively infrequent, but serious, adverse events we propose the following:

1. Establishment of product-specific registries to prospectively follow a cohort of RA patients who receive the newly approved therapy. These registries should be created and maintained by the sponsor, and periodically reported to regulatory agencies, as required, per postmarketing approval; and
2. Development of a much larger cohort of RA patients treated with multiple second line agents, of sufficient size to enable case-controlled determinations of the relative incidence of rare but serious events in the treated (registry) versus the larger disease population. Such design considerations must assume statistical estimates of standard power (80%) and degrees of confidence (95%). See Figure 1.

ORGANIZATIONAL DIMENSIONS

The number of patients necessary for agent-specific registries and a larger patient population adequate to supply a matched case-control cohort will depend upon estimates of the detectibility of an increased incidence over background. Small increases, such as 1.5-fold (1.5×), will require prohibitively large sample populations; such differences arguably may not be clinically important. On the other hand, very

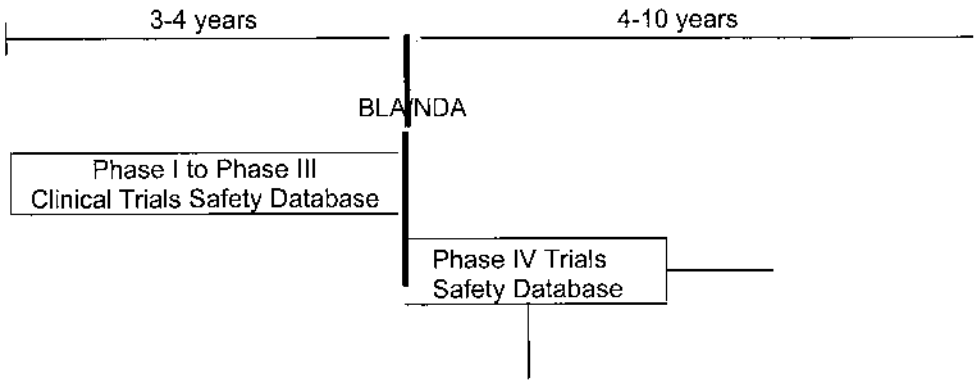

Figure 1. Schematic for capturing adverse events data. BLA: biologics license application; NDA: new drug application.

large increases, such as 20×, will likely be detected on the basis of clinical trials conducted prior to approval of an experimental agent.

We have therefore chosen a 3× to 5× range of detection to illustrate this proposal: assuming a background incidence of LP disease in RA to be 1 per 1000 patients per year. The number of patients and controls needed if the experimental agents impart an additional constant 5-fold risk over background (hazard rate), would be about 600 patients and at least 600 controls (in a 5 year study).

Further, determinations of the relative incidence rates require patient-pairs matched for all major risk factors for the adverse event of interest. Because recognition of many of these events of concern has only recently emerged, or remains limited, we must account for as many possibilities as feasible. Currently, we are not able to distinguish between, for example, disease duration, number of prior therapies, and types of prior treatments (e.g., immunosuppressive vs other). Thus the "control pool" must be sufficiently large to accommodate at least 2, or possibly 3, simultaneous predispositions. And we must assume that once the new agent is approved for use, at least some of the "case-control" patients will be treated with it, thus confounding the data. Taking the above factors into consideration, we estimate it will be important to identify a minimum of 3 case-controls for each patient in the product-specific registry.

Admittedly, alternatives to establishment of such a large patient cohort population exist, but they are limited in several ways. Although investigators may be encouraged to enrol one or more "matched" patients at the time of treatment of another individual with the same disease, this is a limited sample that may not reflect a true disease population. Large, established databases, as are available through Medicaid in the United States or through government organizations in some European countries (Sweden), can theoretically provide a sufficient sample size. However, data regarding verified diagnosis and treatment are often lacking, and detailed reviews of medical records, which may be prohibitively expensive, are frequently required to accurately extract this information. Further, these databases may not offer a representative sample of RA patients. Other established databases exist, such as ARAMIS (Arthritis, Rheumatism and Aging Medical Information System) or the ARC (Arthritis and Rheumatism Council) that have made important contributions to our understanding of differences in NSAID toxicity[22], the role of disease modifying agents in influencing longterm outcomes[23], and incidence of malignancy[24]. These databases are directed at existing compounds. It would be envisaged that these databases could be used as collaborations for any new longterm project that emerges from these discussions.

The intent would be to monitor patients entering treatment with the experimental agent, collecting sufficient data to adequately assess the incidence of identified adverse events. Simultaneously, the sponsor could choose to establish a matched cohort of untreated patients, drawn (and matched by 1–2 important risk factors) from each investigator's larger patient population. Although this practice offers a reasonable control group, many of these patients will subsequently become eligible for treatment with the new agent once it is approved, thereby limiting the value of this matched cohort. Therefore it would be important to establish an additional patient population to serve as a "control group" for the patient registry at the time of product approval. This approach could present significant pragmatic limitations, unless a large patient cohort was available from whom individuals matched for several predisposing risk factors could be drawn.

OPERATIONAL STRUCTURE

An umbrella organization (developed by the OMERACT Toxicity Working Group under the auspices of international and regional rheumatology leagues ILAR, EULAR, PANLAR, AFLAR, and APLAR) would be responsible for establishment of this large patient cohort, envisioned to be drawn from around the world. This organization, overseen by a coordinating committee of epidemiologists, statisticians, and data managers, would function in collaboration with participating pharmaceutical and biotechnology companies. They would seek to enrol a control pool of patients sufficient to enable matching by several known or highly likely risk factors. This research could be accomplished by surveying rheumatologist members of each national rheumatology association for patients with confirmed diagnoses of RA in whom all prior treatments could be determined. Once enrolled, patients would be surveyed by postcard, telephone, or the Internet on a yearly basis regarding recent therapies and development of signs and/or symptoms consistent with rare adverse events possibly associated with treatment of RA. Data might also be submitted by the patient's rheumatologist or primary care physician. Issues such as the movement of patients and the variation in reporting of some endpoints (particularly death) between countries would need to be addressed.

SPONSOR (PHARMACEUTICAL COMPANY)

Each sponsor would be responsible for establishment of the patient registry for its product, entering this data into the confidential product-specific database managed by the sponsor. The umbrella organization would function to provide a matched (cohort) database, which would be surveyed yearly in the context of surveying all members of the database. The sponsor would contract with the umbrella organization to provide all appropriate information from the cohort group to test the hypotheses regarding meaningful (3–5×) increases in serious adverse events over background. This would occur on a semiannual basis, timed with the

yearly reporting of findings in the product-specific registry required of the sponsor. The process should continue indefinitely, but a 10 year point is used here to gain insight into the rare events of concern. It is expected that sufficient funding to maintain this large (cohort) database could be derived from providing the contracted services to the participating sponsors. It is expected that findings of interest that may develop in the large cohort database will be made available to the general rheumatology community.

It is also hoped that the sponsor might contract with the umbrella organization to maintain and survey the patients enrolled in its product-specific registry. Indeed, this may be extremely desirable, first since true comparability requires exactly identical procedures, and second because an outsourced data collection may be viewed as more credible. This remains a choice between individual companies and the umbrella organization, and would not be an essential requirement for participation in the larger cohort matched surveillance program, offered on a "fee for service" basis.

It would remain the responsibility of the sponsor to report serious adverse events to the regulatory agencies. The umbrella organization would report all significant adverse events occurring in its "control" cohort population promptly to sponsors, as well as supply periodic overall adverse event incidence data from that group of patients.

These ideas are presented to stimulate discussion on a very important aspect of novel antirheumatic drug development. This proposal has since been further developed at OMERACT 5 (Toulouse, April 3–5, 2000) and it is hoped that all those wishing to comment will do so.

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