Workshop Report - Part 1:

Toxicity of Antirheumatic Drugs

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A number of research questions were put to each of the workshops. Participants were asked to address these questions in the light of data on toxicity and toxicity measurement presented by the lead speakers and from the papers already circulated. Workshops were asked to focus on 3 types of studies - those published in peer reviewed journals, pharmaceutical company data (not published), and pharmacoepidemiological studies.

Research questions were as follows:

1. How can your type of study (published, pharmaceutical data, or pharmacoepidemiological) be improved in terms of producing toxicity data, i.e., are there design issues of importance, are there reporting issues, etc?

2. How can results of these studies be communicated (operationalized, put into practice)?

3. Is there a toxicity index to be used, i.e., a current one, or should we be designing a new one?

The workshops raised a number of issues: (1) Cohorts of family physicians are involved in good quality studies or in audit programs; (2) Managed care groups are now beginning to amass large amounts of data on particular disease groups; (3) Continuing medical education activities of physicians offer a good opportunity to involve physicians in studies or programs to review toxicity/benefit tradeoffs; (4) Regulatory and other government agencies have an enormous amount of information that is underutilized with respect to the analysis of drug toxicity; and (5) Community and hospital pharmacies are also able to provide large amounts of information on drug use.

There was discussion on the variable quality of forms used to record adverse events, depending on the origin of the study. Pharmaceutical companies have developed standardized high quality forms, and US Food and Drug Administration (FDA) representatives described the current US practices for adverse event reporting in pre and post-marketing clinical trials. Changes are occurring coincident with efforts at international harmonization (International Conference on Harmonization Guidelines, ICH). Currently a new adverse event form, MEDWATCH 3500, has been developed for reporting adverse events ascribed to administration of drug, biologic agent, or device. Its use is recommended, and will likely become required, as additional recommendations are incorporated in the US Code of Federal Regulations (CFR). US CFR definitions of serious and/or unexpected adverse events and required reporting times will be modified to conform with ICH guidelines. Concerns raised the the fialuridine trials in the US have led to additional suggestions. These include several clinical study design elements: prospective estimates of expected deaths and serious adverse events; emphasis upon inclusion of an appropriate control group, especially when underlying disease may produce adverse events that could be confused with drug toxicity; longterm safety followup after completion of protocol and use of independent assessors to evaluate safety and monitor protocol compliance. It was felt that there could be more standardization of case report forms/toxicity measures - across centers and across trials, and with careful attention to the issues of cultural and language differences and the different perceptions of doctors, industry, and government as regards adverse reactions. Despite efforts among the regulatory authorities and WHO for international harmonization, issues of uniform reporting methods still exist within countries. In company sponsored clinical trials, the adverse event case report forms previously used varied greatly. As authorities such as the US FDA began to require single formats of minimally acceptable information, these case report forms have evolved to solicit the required data (timing of event, relationship to other medications, causality, and attribution) in similar fashion. Nonetheless, variability exists in how the data supplied by the investigator are "translated" by the company into accepted dictionary terms to allow computer coding and interpretation across multiple trials of the same therapeutic agent. Some of this variability has occurred when symptoms and not diagnoses are reported by the investigators, some when attempts are made to harmonize dictionary terms from different countries. Clearly, WHO, ILAR and OMERACT efforts could be helpful in this process.

It was felt that an inventory of forms carried out by ILAR-OMERACT might be appropriate — to this end, it was thought that a working party could be established between ILAR-OMERACT and industry to explore the

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methodology for an adverse drug reaction form inventory and access to adverse reaction material. It was gratifying that industry representatives indicated a willingness to allow access to data, assuming that some sort of control was maintained to protect proprietary information. There would obviously be differences in the attitude of industry to allowing this data to be seen, depending on the stage of drug development. There might be certain benefits through better access to industry data in terms of improving standards of clinical practice and potentially developing a more useful "label" for the drug product. The groups discussed the types of studies that might be used to record adverse events. These included cohort, record linkage, and spontaneous reporting, which all had a place. It was also felt that the value of the properly run randomized controlled trial postmarketing had been overlooked because it was assumed that these were often too hard or too costly to perform. Finally, it was felt that longterm studies were of great importance in rheumatic diseases for reporting adverse events under controlled conditions, rather than producing adverse reaction data from principally short term studies.

It was appreciated that OMERACT had established a core set of efficacy variables in rheumatoid arthritis and other rheumatic disorders, and it was strongly felt that a core set of toxicity measures needed to be established for antirheumatic drugs. There did not seem to be enough awareness or use of some of the large international databases, e.g., the WHO Cooperative Centre and Database for Adverse Drug Reactions. Again, it would seem appropriate that the ILAR-OMERACT group work closely with this center.

Another issue that became clear during the discussions was the need to report adverse event data in a more uniform and detailed manner. This was emphasized by the difficulty in obtaining comparable data across published studies to perform accurate meta-analyses of toxicity. Authors are encouraged to describe fully the numbers and flow of patients by treatment groups throughout the trial; and to clearly report the reasons for dropouts for each group. All adverse events should be tabulated and analyzed, as well as the incidence of adverse events per patient. It was felt that adverse event reporting must include all events observed by the patient or the doctor, and that there must be some harmonization of approach to report these. There was discussion concerning methods of weighting adverse events, for example, that of Fries, using the subjective relative importance placed by groups of physicians on a particular event to provide numerical weightings. This would need to be standardized. Patients have generally been overlooked with respect to providing useful data on cost utility of drugs.

It was suggested that 4 questions be included that use visual analog scales: (1) How helpful has the medication been? (2) How severe is the adverse event? (3) How much more beneficial must the medicine be to continue to take it in the presence of this adverse event? (4) What did you do (or take) when this adverse event occurred, i.e., change in activity of concomitant medications?

Approaches such as visual analog scales, efficacy/toxicity tradeoff assessment with the use of standard gambles or dollar valuations were felt to be quite informative and should be pursued. If specific forms are to be developed to access toxicity data optimally, then clear definitions of the various toxicities must be determined, addressing the issues of face and structural validity of indices.

In terms of research priorities, the groups felt that in the area of toxicity assessment in the rheumatic diseases there must be 4 goals: (1) harmonization of approaches, including the development of a standard dictionary of adverse events (as in the US); (2) better and more complete reporting of adverse drug reations; (3) establish appropriate means of longterm data collection from patients who have completed randomized controlled trials or postmarketing surveillance projects; (4) develop methodology and collect data to understand efficacy/toxicity tradeoffs.

It was noted by a number of groups that current medical practice is often not appropriately informed about efficacy/toxicity tradeoffs or comparisons, despite increased awareness of these issues in the literature. It was felt that a WHO-ILAR-OMERACT study group on toxicity should be established to pursue these issues and report to the next WHO-ILAR meeting and OMERACT meeting.