Report of the 3rd Workshop of European Biologics Registries

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Background and goals of the meeting

Following the release of biologic agents for the treatment of rheumatoid arthritis and other rheumatic diseases, the national societies of rheumatology in several European countries initiated independent registries to observe the long-term outcomes of these new drugs. The registries were established to acquire knowledge on the long-term safety and effectiveness in a broad spectrum of patients seen in daily practice. In order to harmonize the approaches, the European biologic registries have held regular meetings since 2002. After meetings in Manchester/UK in November 2002 and in Stockholm/Sweden in May 2003 the third meeting took place on 22nd January 2004 in Berlin/Germany at the German Rheumatism Research Centre.

The workshop had three major aims

1. To present and contrast the various approaches to register patients on biologics in the European countries (and Canada)
2. To evaluate and discuss initial experiences with the use of register data for satisfying the reporting requirements of the European Medicines Evaluation Agency (EMEA).
3. To harmonize methodological issues including role of a control group of non-biologic treated patients, attribution of events to treatments, coding of adverse events, and interpretation of findings.

The 45 participants were delegates from the existing or planned European registers and Canada and from the companies. Abbott, Amgen, Schering-Plough, Centocor and Wyeth.

The meeting was preceded by a closed meeting of the British, Swedish and German register with the above mentioned companies concerning requirements for EMEA reporting.

In the following, we report very briefly about the present state of the registries.

Update on European biologics registries

Each register participant presented a poster on their current data, as well as an outline of the aims, methodologies and funding of the registry. The key aspects of each poster were presented as five-minutes oral reports and discussed with all participants.

All registries collect data from physicians and patients. All record activity parameters such as the Disease Activity Score, treatment (biologic agents as well as concomittant treatments with dates of start and termination), adverse events, functional status and other aspects of quality of life. Their major aim is to observe the long-term safety of biologic treatments under
usual practice conditions. Most of the registries investigate additional research questions related to the long-term effectiveness including switches of therapy or the cost-effectiveness of the treatments.

The Swedish ARTIS (anti rheumatic therapy in Sweden group) register unifies a number of regional registers built up in Sweden since 1999. The Swedish register has the longest experience in monitoring biologic agents. Comparator data from non-biologic treated subjects are available from different existing cohorts. The Swedish system also permits the linkage of patient data to national cancer, hospitalisation and death registers in order to obtain morbidity and mortality data.

The British Society of Rheumatology biologics register (BSRBR) started in October 2001 and has collected data of more than 5,600 patients. Registration of patients who are prescribed biologics is mandatory for prescription in the National Health Service. A control group (anticipated: 4,000 cases) is recruited in 16 rheumatologic centres across the UK. Follow-up will be five years. The data are linked to national cancer and death registers. Questionnaires are used to obtain other morbidity data.

The Canadian rheumatologists have implemented a post-marketing surveillance system for etanercept and anakinra. The patients are recruited nationwide and followed-up via telephone interview.

The Czech Rheumatological Society is responsible for an observation of patients treated with biologics with 17 participating rheumatologic centres. By the end of 2003, 282 patients treated with infliximab were included.

The Danish database for biological therapies in rheumatology has registered patients treated with biological drugs since October 2000. The Danish Society of Rheumatology and the Institute for Rational Pharmacology are responsible. By October 2003, approximately 700 patients were registered. The data are registered electronically locally and sent for central analysis via CD-Rom.

The Finnish register of biologics ROB-Fin was set up by the Society of Rheumatology in 2001. In September 2003, 544 patients had been enrolled, most of them on infliximab.

The German long-term observation of biologics in RA (RABBIT) was started in 2001 and has recruited approximately. 1,500 cases with a new prescription of a biologic agent and 700 comparison cases with change of a DMARD therapy as controls. The planned observation period will be five years.
The German Etanercept registry for treatment of juvenile idiopathic arthritis collects data of children with JIA in approximately 35 paediatric rheumatologic units. As only etanercept is approved for children this register is presently restricted to one drug. More than 300 children have been enrolled so far.

In the Netherlands, a multi-centre registry on biological agents is currently being set up based on extensive experiences from several longitudinal studies in rheumatoid arthritis.

The Norwegian 5-center DMARD register (NOR-DMARD) has included almost 3,000 new DMARD starts, among them approximately 20% on biologics. It does not follow individual patients but defines each start of a DMARD therapy as a new case.

The Spanish registry for adverse events of biological therapies in rheumatic diseases (BIOBADASER) is run by the Spanish Medicines Agency and the Spanish Society of Rheumatology. In January 2004 it contained information of 3,622 patients from 92 centres most of them treated with infliximab.

In addition, similar registries have been started or are planned in Poland, Slovenia and Greece.

Nearly all registers receive unconditional grants from the four companies producing biologics. The Swedish, British and German registers give semi-annual reports on adverse events to the companies who use them for their reporting obligations to the EMEA.

First experiences with the use of register data for reporting to the EMEA

Panos Tsintis from EMEA expressed the opinion of EMEA/CPMC that registries constitute an important tool in collecting independent safety data. Their contribution to safe use of the products is very much appreciated by EMEA. So far, results reported from registries are in line with known safety profiles of the products.

Agreement on methodological issues

Following an update on safety of the biologic agents by Kimme Hyrich from Manchester (published in Ann. Rheum. Dis, Jul 2004), Lars Klareskog outlined the importance of control data, Joachim Listing discussed methodological problems in the assignment of events to treatments, and Sonja Kary described problems in coding adverse events with MedDRA. A report was given of the agreements achieved the day before between the three registries mentioned above and the companies concerning reporting of adverse events.

The workshop participants agreed on the following essentials:

All registries should aim at gathering control data from patients not on biologic agents in order to put the events observed into context. However, as these patients will likely have less
severe disease and less treatment failures in their history, comparisons should be made with caution and adjustments to control for the confounding by indication bias should be made.

In the assignment of events to treatments three approaches are possible in principle: the intent-to-treat approach where all events are assigned to the first biologic therapy. This approach is useful in evaluating short-term outcomes. The registries, however, are long-term ventures and changes in treatment are frequent. Therefore, it was agreed that usually an event should be attributed to the last drug received before the event. This latter approach is not appropriate to observe the long-term hazards of drugs such as the development of lymphoma or solid cancers. In these cases the event should be attributed to each biologic drug ever given. It is of vital importance, however, that all registries document carefully the times under each therapy and the dates of occurrence of events.

Adverse events should be coded in a uniform manner using the medical dictionary MedDRA. This dictionary is not ideal but it represents the present standard and is required by regulatory authorities. Due to the very high licence costs it will probably not be possible for all countries to work with this system. Presently the British and the German registries are using MedDRA. A working group will define which MedDRA terms are of specific interest and how they translate into the agreed “Manchester template”. This template is the format in which the three registries who contribute to the EMEA reporting present their semi-annual data.

In the discussion with the companies it became obvious that the registries represent a novel approach for Pharmacovigilence which requires changes in the normal routines within the companies. When receiving information of a serious adverse event from clinical trials or from spontaneous reporting the pharmacovigilance departments will try to get any information available in order to establish whether the event is related or unexpected. By contrast, the registries are epidemiologic outcome studies and will record any adverse event independent of the question whether it is related or unexpected. Reporting from the registries is therefore much more comprehensive than spontaneous reporting. As a consequence, the possibilities to obtain extensive information on each single event are limited. Reporting to the companies and to the regulatory authorities is therefore restricted to the data gathered routinely with the standard record forms. There was agreement that in most cases these informations are sufficient. There are, however, serious adverse events that should be investigated in more detail. These are: serious infections, in particular tuberculosis, demyelinating diseases, aplastic anaemia/pancytopenia, congestive heart failure, lymphoma and solid cancers. In these cases, the registers will enquire additional information from the treating physician. In all other cases there will be no additional queries from the companies.
The participants of the workshop agreed that these meetings are of high value and should be continued. There will be one annual meeting with all European initiatives and a second meeting of the three registries reporting to the EMEA. The next open EULAR meeting will be in May 2005 in Stockholm (date to be fixed).