

REPORT

The British Society for Rheumatology Biologics Register

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Ann Rheum Dis 2005;64:iv42–iv43. doi: 10.1136/ard.2005.042499

The British Society for Rheumatology (BSR) established a nationwide register for patients with rheumatological disorders treated with biologic agents. The register is designed as a national prospective study whose primary purpose is to assess long term toxicity from the use of these agents in routine practice. In addition, the data will be capable of addressing the benefits from their use in relation to their toxicity. One specific feature of the BSR register is the recruitment and collection of data from a parallel comparison group, comprising patients with active rheumatoid arthritis treated with conventional disease modifying agents. Both class specific and drug specific analyses of the group treated with biologicals are planned.

The British Society for Rheumatology (BSR) produced guidelines for the use of anti-tumour necrosis factor (TNF) agents, published in October 2001. Included in these guidelines was the recommendation that rheumatologists within the UK should register all patients treated on a national register in order to study long term safety. Subsequently in 2002, the National Institute for Clinical Excellence (NICE) approved the use of anti-TNF agents for treating patients with rheumatoid arthritis (RA) within the National Health Service (NHS), and included among its recommendations compliance with registration with the BSR Biologics Register (BSRBR) in order to assess the efficacy and toxicity of these agents in routine use.¹ The companies marketing these agents in the UK agreed to provide financial support to the BSR for the register as a single entity, and the BSR then contracted with the University of Manchester to set up and run the BSRBR. Thus rheumatologists prescribing biologicals for RA within the UK have an obligation to register their patients with the BSRBR.

OWNERSHIP OF THE REGISTER

The register and its data are owned by the BSR and the providers of the service have usual academic rights with regard to the data subject to the BSR's approval. This ensures an independence from the pharmaceutical companies that are funding the BSR to provide the register service.

COMPARISON GROUP

Data on long term adverse events in patients treated with biological agents in routine practice predominantly comes from spontaneous pharmacovigilance reporting systems such as the Med Watch programme in the USA.² However, interpretation of the data emerging from such programmes is limited, not only by the lack of denominator data, but also by the lack of data on the frequency of such events in comparable patients receiving conventional therapy. For example, patients with RA are known to be at an increased risk of developing non-Hodgkin's lymphoma (NHL),^{3,4} with such a risk being highest among those with the most severe disease⁵—the very groups that may be targeted for anti-TNF

therapy. Although the risks of anti-TNF treated patients developing NHL have been calculated in comparison with national incidence rates,⁶ such comparisons do not address the question whether there is a specific increased risk with the use of biologicals. In the UK access to these drugs is limited and hence the design of the register included the establishment of a comparison cohort of patients with active RA, treated with standard disease modifying antirheumatic drugs (DMARDs).

SIZE OF THE REGISTER

The BSRBR was designed to have sufficient power to detect a doubling in lymphoma risk between patients treated with a specific anti-TNF agent and those treated with standard therapy over five years of follow up. Such a design required the recruitment of 4000 patients in each cohort to be followed up for 5 years, allowing for drop outs and switches, say from non-biological to biological treatment. The aim therefore is to recruit 4000 patients for each of the anti-TNF agents based on first use of that drug, as well as 4000 comparison patients.

DATA COLLECTION

Baseline

All patients with a rheumatic disease commencing therapy with a biological are asked to consent to participate in the register. A standard baseline form is completed by the consultant or specialist nurse collecting data on demographics, the 1987 American College of Rheumatology (ACR) criteria for RA, the individual components of the Disease Activity Score (DAS 28), details of all previous and current DMARD therapy, and comorbidity. Collection of radiological data is not part of the register.

The patients are contacted and asked to provide additional data on smoking habits and occupational history and are asked to complete a Health Assessment Questionnaire (HAQ) and the quality of life instrument Medical Outcome Survey Short Form 36 (SF-36).

Both hard copy and electronic data collection methods are available. The register is predominantly designed as a register for patients with RA but it does provide a facility for registering patients with other rheumatic disorders.

Follow up

All patients are followed for five years, including patients who stopped therapy or who switched to another biological agent. Three approaches to follow up are used:

- Every six months the rheumatologist is surveyed asking for details of any changes in therapy, current disease activity (DAS 28) and specifically the development of any adverse event. Specific questions are asked about certain key events (table 1).
- The patients are surveyed every six months (for three years) and complete a diary asking about any new diagnoses or significant comorbidities. All such reports from the patient or physician are followed by a request for more clinical information from the patient records. The

Table 1 Information requested by BSRBR relating to adverse events

What was the adverse event and date of event?	Details and dates
Was the patient on biological therapy at the time of the new illness?	Y/N
Did the event result in any of the following? If yes, please provide further details	
Death	
Hospitalisation	
IV antibiotics	
Significant loss of function or disability	
Congenital abnormality	
Life threatening	
Was a yellow card completed for this new illness?	Y/N

focus is on serious adverse events defined particularly as leading to hospitalisation based on the list above. All such events are recorded whether or not the physician attributes the event to the therapy.

- All patients are flagged with the UK Office for National Statistics who then notify the register of: any death, with a copy of the medical information from the death certificate and any cancer.

PHARMACOVIGILANCE RESPONSIBILITY

The existence of the register also permits the collection of safety data required by the licensing authorities within Europe based on long term surveillance of patients treated with these agents. All adverse events are coded by the MedDRA scheme and reported to the sponsoring companies within 24 hours of receipt as well as in the form of six monthly Periodic Safety Update Reports (PSUR). The company must then report them to the regulatory authorities.

CURRENT STATUS OF RECRUITMENT

As at March 2005, we have recruited 8455 patients with RA treated with the anti-TNF agents currently licensed in the UK. The comparison patients are currently being recruited from 18 centres in the UK. Recruitment has been slower than that of the biologicals, given the greater demands on those centres agreeing to participate in this voluntary phase (compared with the 'compulsory' recruitment of patients treated with biologicals). The aim is to recruit the 4000 comparison patients by October 2006, and 1199 have thus far been recruited. One concern was the potential that there would be insufficient overlap in disease severity between the two cohorts to adjust for the confounding by indication. Baseline data on the characteristics of the patients in the two groups are shown in table 2 and although the disease in the comparison cohort is less severe than in the biological treated cohort, the large majority in the former would be eligible for biological treatment according to current UK guidelines. Further there is sufficient overlap in severity indices between the groups to allow for the influence of any such differences on the outcomes of interest to be adjusted for in any analysis.

Table 2 Comparison of baseline characteristics of anti-tumour necrosis factor α (TNF α) and disease modifying antirheumatic drug (DMARD) cohorts

	Anti-TNF cohort	DMARD cohort
No of patients	8455	1199
Age in years (mean (SD))	56 (12)	60 (12)
Female (n (%))	6483 (77)	842 (70)
Current smokers (n (%))	1676 (21)	253 (26)
Disease duration (mean (SD))	13.7 (9.4)	9.1 (9.9)
Disease Activity Score 28 (mean (SD))	6.6 (1.0)	5.1 (1.4)
Previous no. DMARDS (mean (SD))	4 (2)	3 (2)
Health Assessment Questionnaire score (mean (SD))	2.1 (0.5)	1.6 (0.8)

ACKNOWLEDGEMENTS

The authors acknowledge the enthusiastic collaboration of all consultant rheumatologists and their specialist nurses in the UK in providing the data used in this report. The substantial contribution of Andy Tracey, Katie McGrother, and Mark Lunt in database design and manipulation is acknowledged. We also acknowledge the support from Dr Ian Griffiths, Chairman of the BSRBR Management Committee, Professors Gabriel Panayi, David GI Scott, and David Isenberg, Presidents of the BSR during the period of data collection for their active role in enabling the Register to undertake its tasks and to Ms Sam Peters, CEO of the BSR and the BSR staff for considerable administrative support.

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The British Society for Rheumatology Biologics Register (BSRBR) receives financial support from the following UK companies marketing biological agents in the UK: Schering Plough, Wyeth Laboratories, Abbott Laboratories, and Amgen. These resources are used by the BSR to provide a research grant to the University of Manchester.

Competing interests: none declared

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