

This is the second annual Newsletter updating people on the BSR Biologics Register and summarizing some of the data presented at the open meeting of the BSR and BHPR Conference at the Edinburgh International Conference Centre on Wednesday 21st April 2004. The full set of slides shown at the open meeting in Edinburgh in April 2004 are available from the BSR website (Members Section - Filing Cabinet) and the BSR Biologics Register website.

The Register now has over 7,000 patients and recruitment continues at the healthy rate of about 400 per month. The landmarks on the evolution of the Register are shown in figure 1.

Register has taken place during 2003 with registration rates being relatively consistent during the past twelve months. The individual agents on the Register are shown in figure 4. Currently 91% of the patients registered have rheumatoid arthritis. Of the remaining 9% approximately half have psoriatic arthritis and one quarter ankylosing spondylitis. There is regional variation in registration (figure 5), the figures having been derived from the number of patients registered per region divided by the estimated number of prevalent cases of rheumatoid arthritis in each region. This

pattern closely mirrors the distribution of rheumatologists within the UK.

Regarding the base-line characteristics of the patients and their adherence to BSR guidelines, 77% of the population were female with a median age of 55. The median number of previous DMARDs was 4. The mean DAS28 prior to therapy was 6.72 (SD 0.97) - the BSR guidelines being DAS28 of greater than 5.2. 94% of the patients commencing on biologic therapy fulfilled the BSR guidelines. By six months 80% of patients were remaining on therapy. Of the patients remaining on therapy, 21% had shown a good response by the EULAR criteria and a further 62% had shown a moderate response to therapy

Since the Register began in October 2001 to June 1st 2004, we have received notification of 50 confirmed deaths in biologic treated patients (via the Office for National Statistics). These have been grouped according to the chapters in ICD10 on the underlying cause of death specified on the death certificate. Causes of death in these patients included infections (n=2), malignancy (n=9), eye/ear disorders (n=1), circulatory disorders (15), respiratory disorders (n=7), digestive disorders (n=5), skin disorders (n=1) and musculoskeletal disorders (n=10). One of the drawbacks of ICD10 is that infections are allocated to the body systems in which they occur. Thus, we looked at all of the death codes and identified where infections had occurred. Of the total deaths, infections had played a part in nearly half (n=24) of the cases.

We looked separately at deaths that occurred in patients who were under 60 years of age. In total, 15 confirmed deaths occurred in patients of this age group. Causes of death in these patients included malignancy (n=6), circulatory disorders (4), respiratory disorders (n=2, both pulmonary fibrosis) and musculoskeletal disorders (n=3). Infections had been involved in four of these cases. There were two lung cancers, one acute myeloid leukaemia and one each of breast cancer, renal carcinoma and ovarian cancer.

<b>2000</b>	<b>Etanercept licensed for RA Infliximab licensed for RA BSR Guidelines published</b>
<b>2001</b>	<b>1st patient entered onto register</b>
<b>2002</b>	<b>NICE guidance (No 36) Anakinra licensed for RA</b>
<b>2003</b>	<b>1850 patients on register (initial target) Adalimumab licensed for RA</b>
<b>2004</b>	<b>&gt;7000 patients on register</b>
<b>2003-2004</b>	<b>Licensed indications extended to AS (infliximab and etanercept) and PsA (etanercept)</b>

Figure 1

The advent of new biologic agents and the ever increasing licensed indications means that the Register is an evolving entity. Because there is no reason to assume that the frequency, pattern and severity of adverse reactions in the non-RA patients will be the same as those in the RA group, the wish is to register all patients but to analyze the non-RA cohort separately.

Since the last Newsletter a Data Monitoring Board has been convened under the Chairmanship of Professor Cyrus Cooper which has the authority to order an in depth analysis of data if it appears that excessive or untoward adverse events are occurring. Recognition of such occurrences does to a large extent depend upon the vigilance of the users of these drugs and scrutiny of the reports at the arc Epidemiology Unit in Manchester.

While the Register captures data on the efficacy of therapies, particularly in relationship to DAS28, the primary purpose of the Register is to monitor for toxicity in the short to long term and the follow up protocol is shown in figure 2, with flagging for malignancy and mortality continuing indefinitely. The quarterly registration rates are shown in figure 3 and it can be seen that the bulk of the activity of the

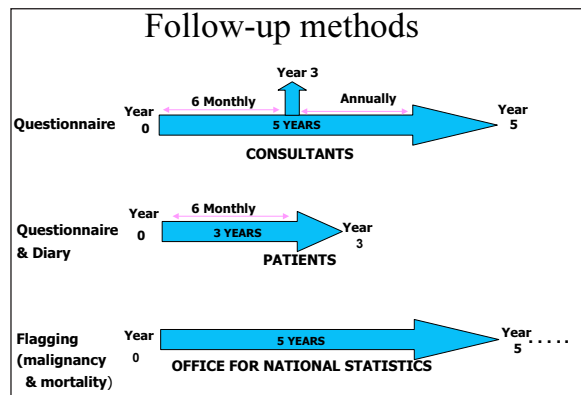


Figure 2

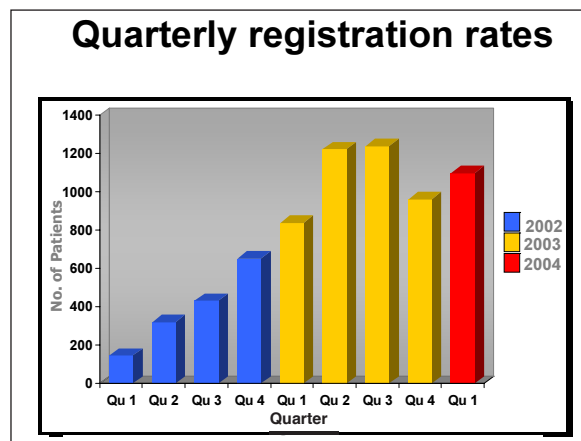


Figure 3

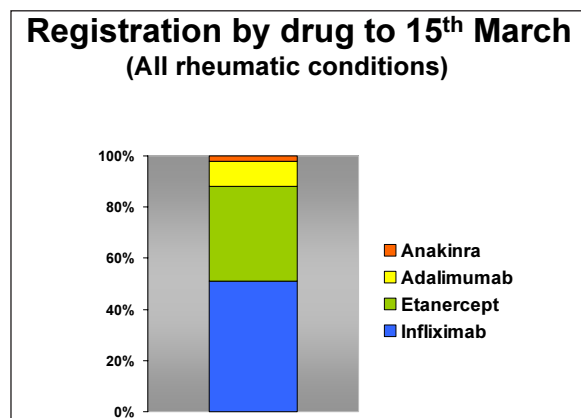


Figure 4

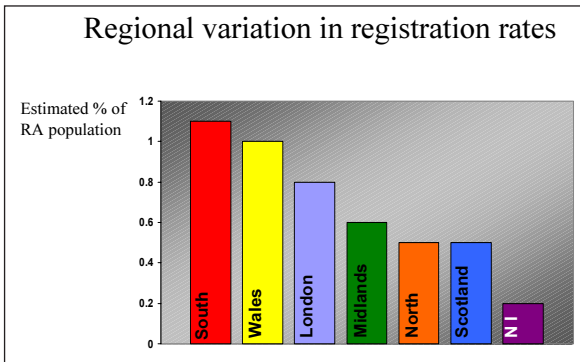


Figure 5

## Pulmonary fibrosis and biologic therapy

Our attention was drawn to a patient who was treated with infliximab plus azathioprine. The patient was known to have mild interstitial lung disease when the infliximab was started and that is why azathioprine was chosen as the accompanying immunosuppressant rather than methotrexate. This patient died from rapidly progressive interstitial fibrosis four months after starting his biologic therapy. Following the notification of this case, we looked through the Register to see if there had been any other similar reports. At the time (March 2004) we found that there were nine patients on the register who were treated with infliximab plus azathioprine and who were known to have pulmonary fibrosis at baseline. Three of these have died, all from lung disease. This is clearly a high death rate and might, at first glance, suggest that infliximab should not be prescribed with azathioprine. However, there are other possible interpretations. It might be the underlying pulmonary disease in combination with the biologic agent which is the problem, rather than the azathioprine combination.

We then went on to look at the mortality rate of all patients on the register who are known to have pulmonary disease at baseline (n=184). The mortality rate amongst this group, regardless of the biologic agent used, was 90 per 1,000 person years follow-up. The mortality amongst patients without pulmonary disease at baseline (n=6,061) was 14 per 1,000 person years of follow-up. After we have adjusted for age and sex, patients with baseline pulmonary disease treated with biologics have a mortality rate 4.4 times higher (95% confidence interval 1.8-10.7) than patients without pulmonary disease treated with biologic agents. We went through a similar exercise comparing the mortality in patients with infliximab combined with azathioprine versus patients receiving infliximab compared with methotrexate. If we adjusted for age, sex and baseline pulmonary disease, then there was no significant difference in the mortality amongst the azathioprine-exposed patients (hazard ratio 1.1, 95% confidence interval 0.1-8.9). These analyses suggest that it is the presence of pulmonary disease, rather than the use of azathioprine which is the cause of the excess mortality.

The comparison cohort of rheumatoid patients treated with conventional DMARDs is not yet sufficiently large for us to provide information on the mortality rate in RA patients with pulmonary disease not exposed to biologic agents.

In accordance with the protocol for the BSR Biologics Register, all this information has been made available to the Data Monitoring Board. It appears that RA patients whose baseline lung disease is suf-

ficiently severe for rheumatologists not to want to prescribe methotrexate with infliximab, have a high mortality. From the data available, we are unable to conclude whether the mortality has been increased or decreased as a result of exposure to biologic agents but we feel that prescribing physicians should be aware of the facts as they stand at the present time. If more information on this becomes available, we will let you know.

## 2004 consultant survey

In February 2004 a postal survey was conducted of all UK consultant rheumatologists enquiring into restrictions that were placed on the use of biologic agents, how the agents were being used and the use of the Register. Overall 60% of people reported some restriction in usage of which funding was the major factor, followed by lack of infrastructure support (figure 6). Currently most patients are identified from routine clinics, rather than going through a systematic screening process of all patients with rheumatoid arthritis.

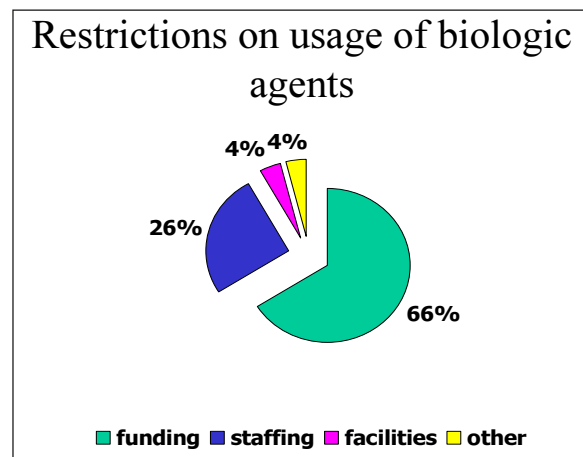


Figure 6

In relation to screening for tuberculosis, 95% of respondents routinely undertook a chest x-ray at base-line but slightly under half performed a Heaf or Mantoux test. In 80% of cases therapy was instigated or given in a Day Case Unit, either rheumatological or shared. From the survey it would appear that about 65% of patients are being entered onto the Register which broadly agrees with figures derived from prescribing data and that percentage is increasing as facilities and staffing improve.

Nurse specialists undertake the majority of documentation relating to the Registry. In general the Register was regarded as efficient and well organised but the major concern was the workload required for documentation and there was a hope that the electronic system would alleviate some of the pressures.

## RheDAS

The RheDAS system ([www.rhedas.net](http://www.rhedas.net)) has now progressed from pilot scheme to being nationally "on-line" and individuals can register via the website. The data collection is identical to the paper collection. Tutorial sessions and telephone support are available. (telephone: 01284 725146) Sixty delegates at the BSR attended workshops and demonstrations of RheDAS. The system also allows for the collection and retention of data, which will be relevant to local clinical governance in the use of biological agents.

## Follow up rates

One area of growing concern is the completion rates for the follow up data. Currently there is a "clinician" non-response rate of approximately 20% at 12 months, increasing to 26% by 18 months. We recognise that the local cycle of documentation, which will usually start from when the patient commences therapy, may be slightly out of synchrony with the Manchester EU cycle which runs from when the patient is registered. However there is no need for patients to attend an outpatient clinic just for documentation and a record of the findings at a visit close to the Manchester follow up will be sufficient. A minimal data set template is available on the BSRBR website on which data can be recorded in anticipation of the 6 monthly review. It is also important to record the 6 monthly data on patients who have discontinued therapy, as one of the central themes of the register is to assess safety both during and after therapy.

All members of the Register Committees are extremely grateful for the considerable hard work undertaken by clinicians and allied health professionals in order to make the Register work. At present the relatively slower rate

of recruitment to the control (non-biologic exposed) group means that it is difficult to interpret the rate of adverse events in the biologics group. With the increasing patient years exposure that are now being accumulated it will soon be possible to make broad conclusions about the efficacy and safety of these agents.