

PROTOCOL

**BSR REGISTER OF ANTI-TNF
TREATED
PATIENTS AND PROSPECTIVE
SURVEILLANCE
STUDY FOR ADVERSE EVENTS**

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INTRODUCTION

All pharmacological interventions in rheumatology, including the use of disease suppressive agents, are associated with adverse side effects in a proportion of patients. Adverse events occurring frequently, early during therapy, will be ascertained during clinical trials and post marketing surveillance studies. Longer term complications, such as malignancy, and indeed all rare events, are unlikely to be detected until large numbers of patients have been treated. There is thus a need to continue observation beyond the treatment period.

Immunosuppressive therapy, in particular, is considered to be a potential risk factor for both malignancy and life-threatening infection. The use of therapies such as azathioprine and cyclophosphamide is associated with an increased risk of lymphoproliferative malignancies in patients with rheumatoid diseases (1-3). Immunosuppressed patients are also at risk of serious infections such as from *Mycobacterium Tuberculosis*, *Pneumocystis carinii* and fungal infections (4). In current clinical practice these small risks are accepted if the potential patient benefit is proportionately greater. Informed prescribing of new agents therefore requires knowledge of the magnitude of risk of such longer-term adverse events.

Long term hazards from new biological agents

A number of new, so called 'biological' agents are now available for disease suppressive therapy in rheumatoid and related inflammatory arthropathies. There are 3 drugs currently available which block the action of TNF α (adalimumab, etanercept and infliximab) and one which blocks the IL1 receptor (anakinra). The anti-TNF α drugs have been shown to be effective in controlling disease activity in rheumatoid arthritis (5-7), juvenile idiopathic arthritis (8), psoriatic arthritis (9) and ankylosing spondylitis (10) for periods of up to one year. They are now licenced for use in all of these conditions. In addition, the drugs are being used on a named patient basis in patients with other inflammatory rheumatic conditions, which are too rare for randomised controlled trials to be practical. Data also suggest these drugs may be effective in slowing the process of erosive damage (11). Their efficacy over the longer term needs to be assessed. Data from clinical trials have reported relatively low levels of toxicity with these drugs and the incidence of adverse events or side effects during therapy, at least in the first few months of therapy, seem to be acceptably low. It might be expected that these agents would impair the immune response to infection but data from isolated case reports of serious infection are difficult to interpret. Similarly there are no data available on the magnitude of any increased risk of lymphoproliferative malignancy in the long-term, although a few cases have been reported. Clinical trials of new agents also exclude many groups of patients at higher risk of infection, for example those with co-morbidities such as diabetes. In routine practice the occurrence of such events may be higher.

It is important to remember, however, that there is an increased risk both of serious infection and lymphoproliferative malignancy in patients with rheumatoid arthritis and other connective tissue diseases, independent of whatever treatment they have received. Thus, it has been clearly established that there is a substantial increased risk of non-Hodgkin's lymphoma in patients with rheumatoid arthritis, associated with long standing active disease (12,13). Similarly, patients with rheumatoid arthritis are at a significantly increased risk of serious infection, and indeed infection is often cited as one of the major causes of excess deaths in this disorder (14,15). Thus the patients most likely to receive the new agents are already at increased risk of infection and malignancy. It is therefore fundamentally important not just to document the occurrence of these events in a treated cohort of patients but to compare their occurrence with that which might have occurred if such patients had remained on "conventional" therapy.

Careful observation of cohorts of patients might show a statistically significant increase in risk either of malignancy or infection. Any such risk would then have to be balanced against the benefits in terms of improvement of quality of life that the introduction of such agents might bring. Furthermore, it is important that surveillance also examines the occurrence of other co-morbidity and mortality. It may

be hypothesised, for example, that long-term effective disease suppression might reduce the all-cause mortality. Increased mortality is a well-recognised feature of rheumatoid arthritis (16,17).

It therefore follows that there is a need for an epidemiologically rigorous surveillance programme, which would evaluate any excess risk in the occurrence of such adverse events after allowing for confounding factors particularly of disease severity and other concomitant therapy. Long term morbidity and mortality event-tracking, over a minimum of 5 years of these cohorts would offer a realistic opportunity of evaluating an increased risk.

OBJECTIVES

The hypothesis will be tested that biologic therapy in patients with rheumatic diseases increases the risk of malignancy, important co-morbidity and severe infection. In developing the methods of a study to test this hypothesis it is assumed that any increased risk will become apparent within 5 years of starting therapy.

The following primary endpoints will be evaluated:

- (i) any malignancy
- (ii) any lymphoproliferative malignancy
- (iii) any infection requiring hospitalisation
- (iv) serious co-morbidity
- (v) death

The following subsidiary hypotheses will be tested:

- (i) any increased risk is related to dose or duration of therapy
- (ii) there are specifically identifiable disease characteristics that act synergistically to increase the risk
- (iii) therapy with multiple biological agents acts synergistically to increase the risk

In addition the benefits of therapy, as assessed by normal clinical indicators, will be compared to any increases in the adverse outcomes listed above.

DESIGN

The study proposed is a series of prospective cohort studies comparing the risk of development, over 5 years, of the endpoint between: (i) an exposed group of patients with one of a list of defined rheumatic disorders newly exposed to a biologic drug and (ii) a comparison cohort of patients with similar disease characteristics exposed to other, but non-biologic, therapies. It is envisaged that there will be a number of exposed cohorts studied, each defined by starting therapy with a particular agent, but that the comparison would be with the same group of non-biologic treated subjects.

METHODS

SUBJECTS

Exposed Cohort

For each biologic drug the exposed cohort will be patients with a rheumatic disease (the most common being rheumatoid arthritis), newly starting therapy with that biologic agent. Inclusion criteria for such subjects are:

- (i) patients with rheumatoid arthritis should either satisfy ACR classification criteria at the time of registration or be classified as having been diagnosed with RA by the consultant rheumatologist.
- (ii) age 16 - 75.
- (iii) willingness to give informed consent for long term follow-up including access to all medical records.
- (iv) minimum of one treatment with a biologic agent.

External validity will be maximised by attempting to ascertain all patients, newly treated with that biologic agent. The support of the BSR with help from the pharmaceutical industry will be necessary to ensure maximal recruitment.

Recruitment will be co-ordinated at a national level. The study will be based in the United Kingdom and the Republic of Ireland.

Non-exposed Cohort

It is accepted that patients treated with biologic therapy will be those with more severe disease. It is assumed, based on both financial grounds, and random variation in clinical practice, that there will be considerable overlap in the severity profile between those patients exposed to a biologic agent and those not exposed. Eight rheumatological centres, representing a broad mix of secondary and tertiary care service provision, and geographical and socio-demographic diversity have been recruited. These are Belfast, Glasgow, Leeds, London (GKT) Stoke-on-Trent, Derby, Norwich and Poole. Other centres have been approached including Manchester Royal Infirmary, Macclesfield District General Hospital, Christchurch Hospital and St Helen's Hospital. Patients will be eligible to be included as non-exposed if they have RA and were started or continued on a new, non-biologic, disease modifying drug within the previous six months.

Each of the centres listed above will submit to the co-ordinating centre, baseline information on all new non-biologic therapy patients together with other relevant clinical and laboratory data. The selected subjects will have already been asked by their local centre for their informed consent to be followed up, as for the exposed cohort.

Comparability of Exposed and Non-exposed Cohorts

The greatest concern with this study is the potential lack of comparability between the exposed and non-exposed RA cohorts in relation to their underlying risk of endpoint development. The recruitment process outlined above will therefore be monitored on a 3 monthly basis and comparisons undertaken between the distributions in the following indicators of severity between the cohorts recruited to both groups HAQ, DAS 28, disease duration. This analysis will be undertaken both on the groups recruited in the preceding quarter as well as on the cumulative experience taking into account any substantive shift from non-exposed to exposed status. An analysis has already been undertaken on

the first 250 subjects recruited to both groups which has shown sufficient comparability between biologic treated and comparison groups (see Appendix) to permit useful analysis. Residual differences will be adjusted for in the analysis.

Sample Size and Recruitment

The recruitment of the Biologic-treated subjects to the Register, for any particular agent, will be determined by a number of external factors. These include:

1. The recommendation by the National Institute for Clinical Excellence (NICE) that all subjects with RA treated with these agents within a specified approval period should be registered.
2. The desire by the sponsoring companies that all treated subjects within a specified period within the UK should be registered to satisfy the requirements of the European Regulatory Authorities (EMA) and its UK arm, the Medicines Control Agency.
3. The uptake of the agents by rheumatological prescribers.

It is likely that the number of subjects treated with any particular agent will vary and therefore the power to detect differences in risk between subjects taking that agent and the comparison cohort will vary by drug. As recruitment for any particular agent increases thus the number of risk hypotheses that can be investigated will increase. The other issue that will influence statistical power is the duration of follow-up. Under a model that proposes that the increased risk of a long term hazard is constant over the duration of follow-up, then the number of person-years at risk increases in direct proportion to the length of follow up.

The current levels of monthly recruitment of subjects treated with their first anti-TNF biologic agent is approximately 350, equivalent to 4200 in a full year. Currently subjects are being treated with one of three anti-TNF agents and including those already registered it is anticipated that by the end of October 2005 there will be some 13000 anti-TNF subjects recruited. Thus by October 2005 there should be approximately 4000 subjects treated with each of the 3 agents. Recruitment may need to continue for any agents either newly licensed or for whom there have been early supply difficulties.

The one recruitment factor that is however under the control of the Register is the size of the comparison cohort. In selecting this, calculations have been based on the ability to detect a doubling in the risk of lymphoproliferative malignancy, the most important of the end-points under study. The underlying risk of such malignancy in a rheumatoid arthritis population is estimated to be 130/100000 pyr. For a significance level of 5% (two sided), and power of 80%, the following sample sizes can be calculated to detect the relative risks as shown:

Relative Risk	Exposed <i>Person Years</i>	Non-Exposed <i>Person Years</i>
2.0	19600	19600

Thus allowing 5 person years of follow up per subject, we need to recruit 3900 comparison subjects for this rare endpoint. Loss to follow up is not an issue as all subjects will be flagged with the National Cancer Register. Recruitment to the control centres is anticipated to be 120 per month or 1440 in a full year. Including those currently recruited we aim to reach the target of 3900 by April 2006

As discussed above the experience from the non-exposed cohort will be used as the comparator for all the biologic drugs, unless there was a major variability in the severity profile of subjects commenced on the different therapies. There will be inevitably a large number of subjects exposed to multiple agents, which renders sample size calculations difficult. This will need to be adjusted for in

the analysis and allowance made for possible interactive effects. These are difficult to detect and the sample sizes needed to detect interactions can be enormous. It thus seems prudent to ensure the sample sizes discussed above are the minimum target recruitment. .

Notification of Cases

It will be the responsibility of the referring rheumatologist to obtain patient consent prior to notification. Patient information sheets, consent forms (see Appendix) and a copy of this protocol will be made available on the ARC Epidemiology Unit's and the BSR's website or directly from the BSR. Receipt of notification would then act as the initiating event for the collection of the baseline data, recruitment of comparison subjects and all necessary follow up.

Core baseline data

The following information will be collected (see Appendix) by the recruiting clinician, using a standardised form on the exposed and unexposed controls selected for long term follow-up:

- (i) diagnosis (including the presence or absence of those features listed in ACR criteria for RA)
- (ii) age, gender, month/year recalled symptom onset
- (iii) previous drug history of disease modifying agents, including duration of therapy, maximum dose, reason for discontinuation
- (iv) significant co-morbidity
- (v) all current therapy
- (vi) findings necessary to calculate the DAS 28
- (vii) HAQ score
- (viii) Height, weight, BP

In addition some personal medical information will be obtained direct from each patient recruited.

FOLLOW-UP

The follow up of both cohorts will be organised by the national co-ordinating centre and undertaken to assess:

- (i) any change in therapy
- (ii) development of any of the end points of interest. These are:
 - mortality
 - malignancy
 - serious infection requiring hospitalisation
 - development of new co-morbidities requiring referral to hospital

Follow up will be via the recruiting clinician and the patient.

Change in therapy

The recruiting clinician will be contacted every 6 months and asked to provide data concerning any change in treatment over the preceding year. This includes, continuation on drug, with details of any change in dose and commencement of any new co-therapy. Annual information on disease activity (DAS 28) will also be collected.

Patients will be contacted every 6 months for the first three years and asked about hospital admissions and new hospital referrals. They will also be asked to complete a HAQ and SF-36 questionnaire.

Ascertainment of endpoints

This will be achieved using a number of complementary approaches:

- (i) All exposed and control individuals will be “flagged” with the National Health Service Central Register and the National Cancer Registry for continuous surveillance and notification of mortality and the development of any malignancy. A copy of the death certificate will be obtained for those who die and a copy of the histology for those who develop a malignancy.
- (ii) A patient-held diary will be used to obtain data of hospital attendance or admission for whatever cause - to include length of stay, reason for admission. This will be used to ascertain cases of infection or serious morbidity. Data from the diaries will be obtained from the patients every 6 months for the first 3 years.
- (iii) The referring physician will also be contacted every 6 months to determine, in parallel with the patient-held diaries, the occurrence of any significant morbid event as well as being asked to verify the data provided from the patients. In cases of infection the clinician will be asked to provide a copy of any micro-biological identification of the causative organism

Initial follow-ups to both patients and their physicians will be by post though, depending on local circumstances, contact by email or telephone may be used. Strenuous attempts will be made to follow-up non-responders. At the time of recruitment all participants will be asked to provide the names and contact details of two relatives or friends that could be used to help trace the subject in case of change of address or care-provider. The nature of the National Registration System is such as to ensure near complete follow-up for malignancy and mortality.

ANALYSIS

The initial analyses will consist of comparisons in baseline status between the individuals in the different cohorts. The final analysis of endpoints will be based on comparing the risks of events over time using Cox-proportional hazards regression, taking into account differences between groups as potential confounders and effect modifiers.

Interim Analyses

Interim analyses will be undertaken at appropriate intervals when 5000 person years of exposure have been accumulated in any of the exposed groups. Such analyses will be a guide to the ultimate levels of recruitment and length of follow up required. Decisions as to the timing of publications and the need for continued follow up and/or recruitment can only be taken in the light of results from such analyses. A Data Analysis & Monitoring Board has been established, analogous to a Data Safety & Monitoring Board established for major clinical trials. The DAMB will be independent of the principal investigators and also of any of the pharmaceutical industries involved, and will have the power to request interim analyses and advise on the timing and nature of any publications. The DAMB should include at least one epidemiologist and one statistician.

ROLE OF PHARMACEUTICAL INDUSTRY

The goals of industry and the rheumatological community are similar in seeking accurate estimates of any increased risk of adverse events. It may also be a pre-requisite for drug license approval, that a study such as the one proposed is established. It is accepted that it is beneficial that any study, such as the one proposed, should be independent of any direct industry involvement. Thus decisions on analyses, interpretation and publication should be independent of any industrial contribution. Industry can have a crucial role in stimulating registration after licensing, and also contributing their experience into the nature and type of data to be collected. Aggregated data relating to a particular product will be shared with industry in confidence, though individual identifiable patient data will not be released. A participant company has the option of requesting specific analyses and will be shown drafts of any publications, reports, abstracts or other material prior to submission for presentation or publication. They can ask for clarifications or amendments to such material but the final decision on these would rest with the principle investigators and the DAMB. All the principal investigators and members of the DAMB have to complete an annual ‘Declaration of conflict of interests’, which will be added to all publications.

ROLE OF BSR

BSR will be the owner of the data that emerge from the study. The study co-ordinator will report on an annual basis to such committees or sub-committees that BSR deems appropriate. The membership of the DMEC will be subject to the approval of BSR.

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APPENDICES

1. Letter of MREC approval 01.12.00
2. Patient information Sheet Version 5 dated *****
3. Patient Consent Form Version 5 dated *****
4. Patient data forms (5) (approved 05/03/2003)
5. Abstract submitted to the ACR 2003 (BSRBR: appropriateness of comparison cohort)