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PROTOCOL

**BSR Register of Tocilizumab treated Patients and Prospective
Surveillance Study for Adverse Events**

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1. 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 jiroveci* 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), one which blocks the IL1 receptor (anakinra), a T-cell modulator (abatacept) and one which acts on CD20 antigen of B lymphocytes (rituximab). 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 several years. Recently a new monoclonal antibody, tocilizumab, which blocks the action of IL-6 has also been studied in Phase III clinical trials in patients with MTX-resistant RA.

The efficacy of these new compounds 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-

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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.

For tocilizumab, serious infection and malignancy is one of the relevant safety outcomes, as discussed above. However, cardiovascular mortality remains the leading cause of death in patients with RA. In the controlled trials, increases in fasting mean plasma lipid levels were observed in the tocilizumab-treated groups. These elevations were apparent from the time of first scheduled testing at Week 6 and remained elevated during continued dosing, but without further increases. In the clinical trials with tocilizumab, the frequency of coronary ischaemic events and stroke was very low and there was no evidence that tocilizumab increased the risk of such events. However, in view of the increase of lipid levels, cardiovascular adverse events (myocardial infarction and stroke) are outcomes of interest, especially for longer-term follow-up. BSRBR follows for longer periods relatively unselected groups of RA patients on a biological therapy and should be suited to study the occurrence of serious cardiovascular events.

Careful observation of cohorts of patients is needed to detect any statistically significant increase in risk either of malignancy, infection or cardiovascular disease. If found, such risk would then have to be balanced against the benefits in terms of improvement of quality of life. Furthermore, it is important that surveillance also examines the occurrence of other co-morbidity and mortality. It is possible that long-term effective disease suppression might reduce all-cause mortality. Increased mortality is a well-recognised feature of rheumatoid arthritis (16,17).

It therefore follows that for new rheumatological treatments 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

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factors particularly of disease severity and other concomitant therapy. Long term morbidity and mortality event-tracking of these cohorts over a minimum of 5 years would offer a realistic opportunity of evaluating an increased risk. The study proposed is planned to have sufficient size to detect an increased incidence of a relevant but relatively uncommon event as Myocardial Infarction.

2. Objectives

The major hypothesis to be tested is that tocilizumab therapy in patients with RA may be associated with an increased risk of myocardial infarction and important co-morbidity compared to patients treated with DMARD therapy.

In developing the methods for a study to test this hypothesis it is assumed that any increased risk would become apparent within 5 years of starting therapy.

2.1. Primary objectives

Any important increased risk from tocilizumab for the following primary endpoints will be evaluated:

- a) Serious infection requiring hospitalisation or intravenous antibiotics
- b) Malignancy
- c) Lymphoproliferative malignancy
- d) Congestive heart failure
- e) Cerebrovascular accident
- f) Pulmonary embolism
- g) Myocardial infarction/acute coronary syndrome
- h) Hepatic dysfunction/failure
- i) Serious lower gastrointestinal ulcer/bleeding/perforation
- j) Demyelination/ optic neuritis
- k) Infusion/ immunologic reaction
- l) Aplastic anaemia/pancytopenia/neutropenia
- m) Tuberculosis
- n) Pregnancy
- o) Other serious co-morbidity leading to hospitalization
- p) Death

2.2. Subsidiary hypotheses

The following subsidiary hypotheses will be tested:

- (i) any increased risk is related to duration of therapy

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- (ii) there are specifically identifiable disease characteristics that act synergistically to increase risk
- (iii) previous or concomitant therapy with biological or multiple immunosuppressive agents act synergistically to increase risk

3. Design

The study proposed is a prospective cohort study comparing the risk of development over 5 years, of the endpoints listed above between a recruited group of patients with RA who are recipients of tocilizumab and reference cohorts of patients with similar disease characteristics but who 1) are exposed to other, non-biologic therapies, or 2) other, biologic therapies.

4. Methods

4.1 Subjects

1. Tocilizumab cohort

The tocilizumab exposed cohort will be patients with rheumatoid arthritis registered within 6 months of starting therapy with tocilizumab.

Inclusion criteria for such subjects are:

- (i) diagnosis of rheumatoid arthritis, satisfying the revised ACR classification criteria (this may be reviewed in the light of changes in licensed indications)
- (ii) age 18 and over
- (iii) willingness to give informed consent for long term follow-up including access to all medical records
- (iv) minimum of one dose of tocilizumab

External validity will be maximised by attempting to ascertain all patients, newly treated with tocilizumab who are not yet in the Register. Patients who are already in the Register, and who switch to tocilizumab will also be followed, in line with existing agreements, up to and a maximum of five years after changing to tocilizumab.

The project will be steered by a BSR committee who will encourage members of the society to participate in the project to ensure maximal recruitment across the whole UK. Recruitment will be at a national level.

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Patients recruited who are already registered on the BSRBR, for example having already been treated with an anti-TNF alpha treatment, will be eligible for inclusion if they switch to tocilizumab but will only contribute patient months of follow-up from the start of tocilizumab .

2. Non-tocilizumab cohorts (reference groups)

One comparator cohort will be the RA patients treated with non-biologic DMARDs recruited to the BSRBR from control sites within the UK (until April 2009). Patients who subsequently progress to a biologic agent will, for the purpose of analysis (see below), have their follow-up censored at the time of the first biologic dose, thus they will contribute patient months of follow-up prior and up to the treatment change date.

The second comparator cohort will consist of recipients of other biologic agents; selection to this cohort will reflect types of biologics and duration of treatment found at baseline in the tocilizumab-treated group.

3. Comparability of Exposed and Non-exposed Cohorts

The greatest concern with this study is the potential lack of comparability between tocilizumab and the comparison cohorts in relation to their underlying risk of endpoint development. If there is an important imbalance between key confounders between the groups then this could reduce the likelihood of obtaining robust estimates of risk. The key confounders to be measured at baseline include details of disease severity, including duration, current HAQ, current significant comorbidities and all relevant previous therapies.

All tocilizumab recipients covered by criteria listed above are to be included.

Apart from the comparison with non-exposed cohorts, relation between type of co-medication and outcomes will be considered.

4. Sample Size

Analysis will use various time windows after infusion. A time window of 3 months after infusion should cover the more immediate effects of the drug. The total available follow-up time will however be used for effects that may be delayed, such as the cardiovascular outcomes and occurrence of malignancies. A total of five years of patient follow-up in both tocilizumab and reference groups should become available.

Recruitment to the tocilizumab cohort will depend on external factors including the NICE recommendations for use and the uptake of the agent by rheumatology prescribers. Aim is to recruit a minimum of 500 patients.

An interim analysis will be done when 1000 observation years are completed (i.e. approximately 500 patients followed by a mean of 2 years). This analysis will look

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at crude event rates and if any signal becomes apparent, the DMEC will be consulted. Additional analyses may be done, depending on signal generated. Recruitment will be done over a period of at least 2.5 Y. The main analysis will be done when tocilizumab recipients have had 5 years of follow-up after their first infusion.

After these five years, mortality and occurrence of cancer will be followed via the NHS Central Register and the National Cancer Register.

There will be inevitably be a large number of subjects exposed to multiple agents. This problem will need to be adjusted for in the analysis and allowance made for possible interactive effects

4.2 Registration of tocilizumab treated patients

The policy currently adopted by the BSRBR for the anti-TNF subjects will be followed. The BSRBR will seek an amendment to its Ethical Approval from the North West MREC for an extension to tocilizumab. It is the responsibility of the referring rheumatologist to obtain patient consent prior to notification. Patient information sheets, consent forms (see Appendix 1) 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.

4.3 Collection of Core baseline data

The following information will be collected (see Appendix) by the recruiting clinician, using a standardised form currently used for the BSRBR:

- (i) diagnosis (including the presence or absence of those features listed in ACR criteria for RA)
- (ii) age, gender, year of recalled symptom onset
- (iii) previous drug history of disease modifying agents, including duration of therapy
- (iv) significant co-morbidity
- (v) all current therapy
- (vi) findings necessary to calculate the DAS28
- (vii) HAQ, and EQ-5D, scores
- (viii) Height, weight, BP

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

For those patients who receive tocilizumab on more than 1 occasion pre-treatment scores (DAS28, HAQ etc) will be requested in addition to routine 6 monthly data collection where available.

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4.4 Follow-Up

The follow up of all subjects will be organised by the BSRBR as with the existing subjects recruited and undertaken to assess:

All doses of tocilizumab received

Development of any of the end points of interest. These are:

- Serious infection requiring hospitalisation or intravenous antibiotics
- Malignancy
- Lymphoproliferative malignancy
- Congestive heart failure
- Cerebrovascular accident
- Pulmonary embolism
- Myocardial infarction/acute coronary syndrome
- Hepatic dysfunction/failure
- Serious lower gastrointestinal ulcer/bleeding/perforation
- Demyelination/ optic neuritis
- Infusion/ immunologic reaction
- Aplastic anaemia/pancytopenia/neutropenia
- Tuberculosis
- Pregnancy
- Other serious co-morbidity leading to hospitalization
- Death

Additional analyses will check for potential interactions: occurrence of above events in patients who have tocilizumab with another biologic. Also events will be analyzed separately for group aged over 75 years.

Any pregnancy will be followed for its outcome

Follow up will be via the recruiting physician, the patient directly and by flagging with the national registers for cancer and mortality.

1. The recruiting physician will be contacted every 6 months for the first 3 years and then annually for the next two and asked to complete a standard data form covering any change in treatment over the preceding 6 months. This includes continuation on drug and reasons for stoppage, with details of any change in dose and commencement of any new co-therapy. Clinical information to permit calculation of the disease activity score (DAS28) is also collected. Data are also collected on all new serious co-morbidities occurring in the previous period.
2. Patients will also be contacted every 6 months for the first three years and asked to complete a patient diary (Appendix) which includes data about

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hospital admissions and new hospital referrals. They will be asked to complete a HAQ, and EQ5D questionnaire at these time points.

Following the report of any serious morbidity, either by subject or physician, the referring physician is immediately contacted by the BSRBR and asked to provide further details where available. For specific morbidities of interest certain specific details are requested (Appendix). All serious morbidities are coded by a trained nurse using the MedDRA system, a licensed copy of which is obtained annually, and reported within 24 hours to the sponsoring company

3. 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 details of type and site of cancer for those who develop a malignancy will be provided.

Initial follow-ups of both patients and their physicians are by post with postal and telephone reminders where appropriate. Strenuous attempts are made to follow-up non-responders and non-responders to one follow up are nonetheless (unless further follow up is refused) contacted again at the next follow up point. At the time of recruitment all participants will be asked to provide the names and contact details of a relative or friend 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.

5. 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 will be undertaken at appropriate time intervals when 1000 person years of exposure have been accumulated in the tocilizumab exposed group. Such analyses will be a guide to the ultimate levels of recruitment and length of follow-up. Decisions as to the timing of publications and the need for continued follow-up and/or recruitment can only be taken in light of results from such analyses. A Data Monitoring and Ethics Committee (DMEC) has been established, analogous to a Data Safety and Monitoring Board established for major clinical trials. The DMEC will be independent of the principal investigators and also of any of the pharmaceutical companies involved, and will have the

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power to request interim analyses and advise on the timing and nature of any publications. The DMEC should include at least one epidemiologist and one statistician.

Pharmacovigilance

Serious Adverse Event Reporting for tocilizumab will be done as per protocol of BSR

Role of the 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 prerequisite for drug licence 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 industry 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, via the BSRBR Steering Committee, 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 DMEC. All the principal investigators and members of the DMEC 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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References

1. Asten P, Barrett J, Symmons D
Risk of developing certain malignancies is related to duration of immunosuppressive drug exposure in patients with rheumatic diseases *J Rheumatol* 1999; 26: 1705-14
2. Radis CD, Kahl LE, Baker GL et al
Effects of cyclophosphamide on the development of malignancy and on long-term survival in patients with rheumatoid arthritis *Arthritis Rheum* 1995; 38: 1120-7
3. Kinlen LJ, Sheil AGR, Peto J, Doll R
Collaborative UK-Australasian study of cancer in patients treated with immunosuppressive drugs *BMJ* 1979; 2: 1461-6
4. Furst DE, Clements PJ
Immunosuppressives in Rheumatology (2nd Ed) edited by Klippel JH, Dieppe PA Mosby (New York) 3.9.1-10
5. Maini RN, St Clair EW, Breedveld F et al
Infliximab (chimeric anti-tumour necrosis factor α monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomised phase III trial *Lancet* 1999; 354: 1932-9
6. Moreland LW, Schiff MH, Baumgartner SW et al
Etanercept therapy in rheumatoid arthritis *Ann Intern med* 1999; 130: 478-86
7. Weinblatt ME, Kremer JM, Bankhurst AD et al
A trial of etanercept, a recombinant tumour necrosis factor α receptor: Fc fusion protein in patients with rheumatoid arthritis receiving methotrexate *N Engl J Med* 1999; 340: 253-9
8. Lovell DJ, Giannini EH, Reiff A et al
Etanercept in children with polyarticular juvenile rheumatoid arthritis. Paediatric Rheumatology Collaborative Study Group. *N Engl J Med* 2000; 342: 763-9
9. Mease PJ, Goffe BS, Metz J et al
Etanercept in the treatment of psoriatic arthritis and psoriasis: a randomised trial *Lancet* 2000; 356: 385-390
10. Braun J, Brandt J, Listing J et al
Treatment of active ankylosing spondylitis with infliximab: a randomised controlled multicentre trial *Lancet* 2002; 359: 1187-1193
11. Lipsky P, St Clair W, Furst D et al
54-week clinical and radiographic results from the ATTRACT Trial
Arthritis Rheum 1999 42; (Supplement) S401 (Abstract)
12. Prior P, Symmons DPM, Hawkins CF, Scott DL, Brown R
Cancer morbidity in rheumatoid arthritis *Ann Rheum Dis* 1984; 43: 128-31
13. Cibere J, Sibley J, Haga M
Rheumatoid arthritis and the risk of malignancy *Arthritis Rheum* 1997; 40: 1580-6
14. Symmons DPM, Jones MA, Scott DL, Prior P
Longterm mortality outcome in patients with rheumatoid arthritis: early presenters continue to do well *J Rheumatol* 1998; 25: 1072-7
15. Mutru O, Laakso M, Isomaki H, Koota K
Ten year mortality and causes of death in patients with rheumatoid arthritis
BMJ 1985; 290: 1797-9

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16. Kvalvik AG
Mortality in rheumatoid arthritis *Rheumatology in Europe* 1996; 25: 9-14
17. Wolfe F, Mitchell DM, Sibley JT, Fries JF et al
The mortality of rheumatoid arthritis, *Arthritis Rheum* 1994; 37: 481-94