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PROTOCOL

British Society for Rheumatology Biologics Register

A longitudinal observational study of patients with rheumatoid arthritis treated with biologic agents, and prospective surveillance study for adverse events

Certolizumab substudy

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Version 3

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1. Introduction

All pharmacological interventions in rheumatology, including 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 for periods longer than those encompassed in clinical trials and indeed beyond the treatment period if the drug is discontinued for any reason.

Immunosuppressive therapy 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 rheumatic diseases (1-3). Immunosuppressed patients are also at risk of serious infections such as *Mycobacterium Tuberculosis*, *Pneumocystis jiroveci* and fungal infection (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.

1.1 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. The anti-TNF α drugs have been shown to be effective in controlling disease activity in rheumatoid arthritis (RA)(5-7), juvenile idiopathic arthritis(8), psoriatic arthritis(9) and ankylosing spondylitis(10) for periods of several years.

Recently a new anti-TNF, Certolizumab pegol, has been approved for use in RA in the UK. Certolizumab pegol (Cimzia, UCB Pharma) is a pegylated TNF- α -specific Fab fragment of a humanised monoclonal antibody. It binds with high affinity to both soluble and membrane-bound TNF- α , thereby inhibiting TNF- α activity. Results from phase III clinical trials have shown certolizumab to be effective and well tolerated in patients with RA (11-13).

The efficacy of any new biologic 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

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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.

1. 2 Need for a comparison cohort

It is important to remember, however, that there is an increased risk of premature mortality, serious infection and lymphoproliferative malignancy in patients with RA and other connective tissue diseases, independent of the 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 RA, associated, in particular, with long standing active disease(14;15). Similarly, patients with RA are at a significantly increased risk of serious infection, and indeed infection is one of the major causes of premature mortality in this disorder(16;17). Thus the patients most likely to receive the new biologic agents are already at increased risk of premature mortality, 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 or received a different biologic agent.

For certolizumab, the outcomes of interest will be the same as for the existing anti-TNF therapies. In particular, it is important to document whether the risk of serious infection differs between certolizumab and the other anti-TNF agents

1. 3 Balancing efficacy and safety

Careful observation of large cohorts of patients is needed to detect any statistically significant increase in risk either of malignancy or infection. 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-morbidities and mortality. It is possible that long-term effective disease suppression might actually reduce all-cause mortality and lymphoproliferative malignancy.

It therefore follows that for all new biologic 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 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 offers a realistic opportunity of evaluating the relative risk.

1. 4 The British Society for Rheumatology Biologics Register

In October 2001 the British Society for Rheumatology established a nationwide Register (BSRBR) (20) to recruit and follow up all patients treated with anti-TNF α therapies to assess the efficacy in UK Clinics and specifically to investigate whether there were any long term (a minimum of 5 years) risks of serious adverse events over and above those that might be expected in patients with severe RA treated with conventional therapy. Registration of new RA patient starts with anti-TNF α therapy was also recommended by NICE in their technology appraisal about use of these agents in the NHS.

2. Objectives

The major hypotheses to be tested are

1. That certolizumab therapy in patients with RA is associated with a similar risk of developing serious infections compared to patients with similar disease activity receiving other anti-TNF drugs (i.e. patients receiving adalimumab (ADAL), etanercept (ETA), or infliximab (INF).
2. That certolizumab treated RA patients is associated with an increased rate of serious infections compared to the historical non-biologic DMARD cohort.

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

2.1. Primary objectives

The risk associated with certolizumab therapy for the following endpoints (events of special interest – ESI) will be evaluated:

1. Aplastic anaemia / pancytopenia / neutropenia
2. Congestive heart failure
3. Cerebrovascular accident
4. Demyelination /optic neuritis
5. Infusion/ immunologic reaction
6. Lymphoproliferative malignancy
7. Malignancy
8. MI / Acute Coronary Syndrome
9. Pregnancy
10. Pulmonary embolism
11. Serious infection
12. Tuberculosis
13. Death*
14. Hepatic dysfunction/failure
15. Lower GI Ulcer/bleed/perforation

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**All of the above use standard ESI reporting templates apart from death where BSRBR ask for all details leading up to the death.*

New ESIs for certolizumab

- Lupus and lupus-like illness
- Serious skin reaction e.g. Stevens Johnson syndrome, erythema multiforme, toxic epidermal necrosis
- Serious haemorrhage
- Hepatitis B reactivation

2.2. Subsidiary hypotheses

The following subsidiary hypotheses will be tested:

- (i) Any increased or decreased risk for any of the above ESI is related to duration of therapy
- (ii) There are identifiable disease characteristics that act synergistically to alter risk
- (iii) Previous or concomitant therapy with biological or multiple immunosuppressive agents act synergistically to alter risk

3. Design

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

4. Methods

4.1 Subjects

4.1.1 Certolizumab cohort

The certolizumab exposed cohort will be patients with RA registered within 6 months of starting therapy with certolizumab.

Inclusion criteria for such subjects are:

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- (i) Physician diagnosis of RA or satisfying the revised ACR classification criteria (this may be reviewed in the light of changes in licensed indications)
- (ii) Age 18 years 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 certolizumab

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

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 and engagement in the analysis programme

4.1.2. Non-certolizumab cohorts (reference groups)

The first comparator cohort will be patients recruited to the BSRBR with RA who have been registered within 6 months of first exposure to an anti-TNF drug. These patients will be recruited during the same calendar period as the certolizumab cohort. For analyses, patients who switch to a second biological will have their follow-up censored at the time of switching treatments

The second comparator cohort will be the historical RA cohort of patients treated with non-biologic DMARDs recruited to the BSRBR from control sites within the UK (until end of 2008). 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.

4.1.3. Comparability of exposed and non-exposed cohorts

The greatest concern with this study is the potential lack of comparability between certolizumab 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

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baseline include details of disease severity, including symptom duration, current HAQ, current significant comorbidities and all relevant previous therapies. Analyses undertaken to date comparing the anti-TNF alpha cohorts with the standard DMARD group have not revealed any serious imbalance that cannot be adjusted for in subsequent analyses. A similar situation is anticipated with the cohort recruited to the certolizumab group.

All certolizumab recipients covered by criteria listed above will be included. In addition to the comparison with non-exposed cohorts, relation between type of co-medication and outcomes within the certolizumab cohort will also be considered.

4.1.4. Sample Size

The sample size calculation is based on the comparison of certolizumab with the reference groups. It is based on person-time and assumes 5 person years of follow up per subject recruited. An initially non-exposed subject who, during follow up, commences therapy with a biologic agent, then becomes censored for the purposes of analysis. Their subsequent disease experience may count towards the exposed person-years at risk. Loss to follow up, including death from an unrelated cause, will also reduce the available person years. The sample studied needs to be large enough and the subjects followed for a sufficient period, to detect an increase in the incidence of those key adverse events considered of interest. The certolizumab sub-study needs to be able to detect (i) a similar rate of infection in the certolizumab cohort compared to the anti-TNF cohort and (ii) an increased rate of infection compared to the historical non-biologic DMARD cohort.

(i) To test for equivalency with other anti-TNF agents (based on 2 cohorts, one certolizumab and one anti-TNF)

Current analysis suggests that the risk of infection is highest in the early months of treatment with anti-TNF (around 5.0/100 pyrs) but then slowly reduces to around 4.2/100 pyrs at 5 years. The initial analysis of the certolizumab sub-study will include the early months of treatment. Assuming an average background rate of infection in the anti-TNF cohort (i.e. non-certolizumab patients) of 4.5/100 person years and that, for a two-sided test, $\pm 1/100$ pyr infections either side (i.e. 3.5-5.5/100 pyrs) is equivalent, it is estimated that 6,791 person years of exposure are needed in each cohort (assuming 80% power and 5% significance). If the background rate is reduced to 4.0/100 pyrs, it is estimated that 6,068 pyrs would be required. If the background rate is increased to 5.0/100 pyrs, 7,505 pyrs would be required.

(ii) To test for an increased risk of infections compared to the historical DMARD cohort

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Using the most recent BSRBR estimates on incidence of 3.2/100 pyrs in the DMARD cohort and 4.2/100 pyrs in the anti-TNF cohort (80% power, 5% significance), a sample size of 5,626 pyrs is required to confirm this difference (which gives a relative risk of around 1.3) as statistically significant.

To accommodate both of these sample size calculations and allow for loss to follow-up, switching and drug discontinuation, we will aim to recruit 1750-2000 certolizumab patients over a three year period and followed-up for a minimum of five years (therefore a total of 8 years follow-up will be available in those patients registered first). This would be compared with a new comparison cohort of 2000 anti-TNF treated patients as well as the existing historical DMARD control cohort.

Recruitment to the certolizumab cohort will depend on external factors including NICE recommendations for use and the uptake of the agent by rheumatology prescribers.

An interim analysis will be done when 3500-4000 observation years are completed (i.e. approximately 1750-2000 patients followed for a mean of 2 years). This analysis will look at crude event rates and if any signal becomes apparent, the DMEC will be consulted. Additional analyses may be done, depending on signal generated. The main analysis will be done when 1750-2000 certolizumab and anti-TNF recipients have had 5 years of follow-up after their first treatment. After these five years, mortality and occurrence of cancer will continue to 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, which renders sample size calculations difficult. This problem will need to be adjusted for in the analysis and allowance made for possible interactive effects. Interactions can be difficult to detect and require large sample sizes. It thus seems prudent to ensure the sample sizes discussed above are the minimum target recruitment.

In practice the rate of usage of certolizumab for RA in the UK can not be predicted. There are approximately 500 rheumatologists in the UK and to achieve a recruitment of 1750-2000, assuming a compliance of registration of around 80%, each rheumatologist would need, on average, to start 5 patients on certolizumab during a period of 3 years.

4.2 Registration of certolizumab 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 include treatment with certolizumab. It is the responsibility of the referring rheumatologist to obtain patient consent prior to

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notification. Patient information sheets, consent forms (see Appendix 1) and a copy of this protocol will be made available on the Arthritis Research UK 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) NHS number
- (ii) Diagnosis (including the presence or absence of those features listed in ACR criteria for RA)
- (iii) Date of birth, gender, year of recalled symptom onset
- (iv) Previous drug history of disease modifying agents, including duration of therapy
- (v) Significant co-morbidity
- (vi) All current therapy
- (vii) Findings necessary to calculate the DAS28
- (viii) HAQ and EQ-5D scores
- (ix) Height, weight, BP

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

4.4 Follow-Up

The follow up of all subjects will be organised by the BSRBR and will include:

- (i) Number of doses of certolizumab received
- (ii) Development of any of the end points of interest. These are:
 - 1. Aplastic anaemia / pancytopenia / neutropenia
 - 2. Congestive heart failure
 - 3. Cerebrovascular accident
 - 4. Demyelination /optic neuritis
 - 5. Infusion/ immunologic reaction
 - 6. Lymphoproliferative malignancy
 - 7. Malignancy
 - 8. MI / Acute Coronary Syndrome
 - 9. Pregnancy
 - 10. Pulmonary embolism
 - 11. Serious infection
 - 12. Tuberculosis

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13. Death*
14. Hepatic dysfunction/failure
15. Lower GI Ulcer/bleed/perforation

New ESIs for certolizumab

- Lupus and lupus-like illness
- Serious skin reaction e.g. Stevens Johnson syndrome, erythema multiforme, toxic epidermal necrosis
- Serious haemorrhage
- Hepatitis B reactivation

Additional analyses will check for potential drug interactions. Also events will be analyzed separately for the 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 thereafter and asked to complete a standard data (Appendix) form covering any change in treatment over the preceding 6 months/year. This includes continuation on drug and dates and reasons for stopping, 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) will also be collected. Data will also be collected on all new serious co-morbidities and SAEs occurring in the previous period.

The DAS28, HAQ and EQ-5D will be collected to correspond, as closely as routine clinical practice allows, with the scheduled follow-up dates. Specific to the certolizumab cohort, due to the nature of the patient access scheme (first 12 weeks of treatment are free of charge); the DAS28 measured at 3 months will also be collected at the 6 month follow-up. This information will allow for changes in disease activity to be included in statistical outcome models. It will also allow a capture of treatment effectiveness at 3, 6, and 12 months during routine clinical practice, to be included in a study of predictors of treatment response (e.g. prior anti-rheumatic treatment, disease and demographic factors).

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 hospital admissions and new hospital referrals. They will be asked to complete a HAQ, and EQ-5D questionnaire at these time points.

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Following the report of any serious morbidity, either by subject or physician, the referring physician will immediately be contacted by the BSRBR and asked to provide further details where available. For specific morbidities of interest certain specific details will be requested (Appendix). All serious morbidities will be 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 comparison 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 will be by post. Strenuous attempts will be made to follow-up non-responders and non-responders to one follow up will nonetheless (unless further follow up is refused) be 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 3500-4000 person years of exposure have been accumulated in the certolizumab exposed group. 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 light of results from such analyses. A Data Monitoring and Ethics Committee (DMEC) has been established by the BSR, analogous to a Data Safety and Monitoring Board established for major clinical trials. The DMEC is independent of the principal investigators and also of any of the pharmaceutical companies involved, and has the power to request interim analyses and advise on the timing and nature of any publications. The DMEC includes at least one epidemiologist and one statistician.

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Pharmacovigilance

Serious Adverse Event Reporting for certolizumab will be done as per protocol of BSRBR

Role of the Pharmaceutical Industry

The goals of industry and the rheumatological community are similar in seeking accurate estimates of any altered 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 rests with the principal 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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CONFIDENTIAL

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