National Patient Safety Agency

National Research Ethics Service

NOTICE OF SUBSTANTIAL AMENDMENT

For use in the case of all research other than clinical trials of investigational medicinal products (CTIMPs). For substantial amendments to CTIMPs, please use the EU-approved notice of amendment form (Annex 2 to ENTR/CT1) at http://eudract.emea.eu.int/document.html#guidance.

To be completed in typescript by the Chief Investigator in language comprehensible to a lay person and submitted to the Research Ethics Committee that gave a favourable opinion of the research ("the main REC"). In the case of multi-site studies, there is no need to send copies to other RECs unless specifically required by the main REC.

Further guidance is available at http://www.nres.npsa.nhs.uk/applicants/review/after/amendments.htm.

Details of Chief Investigator:

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Full title of study:	Prospective Observational Study of the Long Term Hazards of Anti-TNF Therapy in Rheumatoid Arthritis
Name of main REC:	North West MREC
REC reference number:	MREC 00/8/53
Date study commenced:	October 2001
Protocol reference *(if applicable),*	Protocol dated 06/10/2003

current version and date:	
Amendment number and date:	

Type of amendment (indicate all that apply in bold)

(a) Amendment to information previously given on the REC application form

Yes *No*

If yes, please refer to relevant sections of the REC application in the "summary of changes" below.

(b) Amendment to the protocol

Yes ***No***

If yes, please submit either the revised protocol with a new version number and date, highlighting changes in bold, or a document listing the changes and giving both the previous and revised text.

(c) Amendment to the information sheet(s) and consent form(s) for participants, or to any other supporting documentation for the study

Yes *No*

If yes, please submit all revised documents with new version numbers and dates, highlighting new text in bold.

Is this a modified version of an amendment previously notified to the REC and given an unfavourable opinion?

Yes ***No***

Summary of changes

Briefly summarise the main changes proposed in this amendment using language comprehensible to a lay person. Explain the purpose of the changes and their significance for the study. In the case of a modified amendment, highlight the modifications that have been made.

If the amendment significantly alters the research design or methodology, or could otherwise affect the scientific value of the study, supporting scientific information should be given (or enclosed separately). Indicate whether or not additional scientific critique has been obtained.

The British Society for Rheumatology Biologics Register (BRSBR) has been collecting data on patients receiving biologic therapy (including the anti-TNF drugs etanercept, infliximab and adalimumab) for rheumatoid arthritis (RA) during routine clinical care since October 2001. One of the main reasons for setting up this study was to determine whether or not treatment with these drugs increases the risk of cancer, and in particular lymphoproliferative

cancers, including lymphoma. This amendment outlines changes to the protocol to help us carry out a more detailed analysis of lymphoproliferative malignancies that have been reported to the BSRBR.

1. Incident lymphomas occurring in the biologics-treated cohort will be reclassified according to the World Health Organisation classification, to determine the subtypes of lymphoma seen in these patients. For these lymphomas the loan of representative paraffin blocks of tumour material and histology reports will be requested from the reporting pathologist. Sections will be cut from the tissue blocks for hematoxylin and eosin (H&E) staining and immunohistochemistry in order to classify all lymphomas in a standardised way. This work will be overseen by Dr Richard Byers, Consultant Pathologist and Senior Lecturer at the University of Manchester, and member of the Manchester Lymphoma Group. All material will be carefully stored at Manchester Royal Infirmary, and remaining tissue returned to the patient's pathologist. (See below under 'any other relevant information' regarding patient consent).
2. The effect of RA disease activity on lymphoma incidence will be explored. Each patient in the biologics cohort with an incident lymphoma will be matched individually to 4 controls from the biologics cohort. The case notes for these cases and controls will be reviewed to determine average and cumulative disease activity from the time of diagnosis with RA. Other supporting information will be collated.

Supporting Scientific Information

Background

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease causing pain, swelling, stiffness and deformity. Patients with RA are known to have an increased risk of certain malignancies, including lymphoma (1). The increased risk of lymphoma may relate in part to chronic immune stimulation. However, duration of disease alone is not enough to account for this risk. Recent work from Sweden has shown that the severity of disease, in particular cumulative disease activity, may be a stronger predictor in patients with RA (2).

Recently, the biologic therapy, anti-tumour necrosis factor (TNF), has been shown to be very effective in treating severe RA (3-5). However, there is still anxiety about the long-term safety of anti-TNF agents, particularly a theoretical risk of cancer. TNF is a cytokine protein of the immune system and plays a critical role in tumour surveillance (6). TNF is being studied as an anti-cancer agent in many types of cancer, including malignant melanoma and soft-tissue sarcomas (7;8). It is also known to promote a T-cell cytotoxic response against certain lymphomas.

Unfortunately, patients who receive anti-TNF therapies are those with the most severe RA and are therefore, already at the highest risk of lymphoma. Therefore, any analysis of cancer risk with these new therapies must account for this background risk. The possibility also exists that those patients who respond to anti-TNF therapies, by way of improved RA disease control, may actually have a lower lymphoma risk over time compared to patients who do not receive the therapy, and therefore, any analysis must also account for changes in disease activity over time.

Patterns of lymphoma have already been studied in large cohorts of patients with RA. This has shown that around 80% of lymphomas are B cell lymphomas, and 50% diffuse large B cell lymphoma. Since it is possible that some types of lymphoma may be increased with anti-TNF drugs, and some decreased, the pattern of lymphoma seen in biologics treated patients may change.

Due to the large size of this national cohort and the recording of all serious adverse events, the BSRBR offers a unique opportunity to study the factors governing the occurrence and progression of lymphoma, including anti-TNF drugs and disease activity.

Hypothesis:
Anti-TNF therapy may increase the risk of developing lymphoma in patients with RA by inhibiting the role of TNF in tumour surveillance.

Aims:
To determine the influence of anti-TNF on incidence, subtype and outcome of lymphoma in RA.
To determine the influence of cumulative disease activity on incidence of lymphoma in patients with RA treated with anti-TNF.

Objectives:
1. To ascertain prevalence and incidence rates of patients with lymphoma who are already consented to take part in the BSRBR (a study to monitor the long-term safety of biologic agents in rheumatic diseases).
2. To determine the subtypes of lymphoma in the biologics cohort by reclassifying them according to the World Health Organisation classification.
3. To examine factors predicting development and outcome of lymphoma in the biologics treated cohort, and in particular the influence of disease activity.

Methods:
The BSRBR is an ongoing national prospective observational study assessing the medium-to long-term safety of biologic drugs in the treatment of rheumatic diseases. To 21/07/09, there have been 15418 biologic treated patients and 3775 DMARD treated controls registered. Extensive clinical information is collected at baseline and at six-monthly follow-up intervals. Patients with lymphoma reported by themselves, their consultant or the NHS Information Centre will be identified from the register.

Pathological classification
1. Rheumatology consultants of live patients with lymphoma diagnosed during follow up in the BSRBR will be contacted via letter (appendix A). This letter will ask that they send these patients a cover letter, an information sheet explaining our intention to review their medical notes and lymphoma pathology specimen and a patient consent form (Appendices B, D and E). Consent will not be sought from relatives of deceased patients (see below in 'Any other relevant information').
2. Once patient consent is received (in the case of live patients) the pathologist will be contacted to request the loan of the tumour tissue block with their accompanying report.
3. Tissue blocks will be reviewed and reported by a Histopathologist at the University of Manchester with an interest in lymphoma.
4. In addition, copies of histology reports and the name and address of the patient's Oncologist/Pathologist will be requested from Rheumatology consultants of all lymphoma patients.

Additional work for the consultant / rheumatology specialist nurse entails reviewing medical records for the above information and postage of this information to the BSRBR, as well as postage of letters with information sheets and consent forms to patients. Postage will be paid for by the University of Manchester

Nested case control study
1. The effect of RA disease activity on lymphoma incidence will be explored. Each patient with incident lymphoma will be matched individually to 4 controls from the

biologics cohort. Controls must be alive and free of cancer at the time of matching. The case notes of these patients and controls will be reviewed to assess disease activity from time of diagnosis of RA. This will be done using information recorded in the patient's case notes including blood results, joint counts (where available), radiology reports and physician's opinion. Average disease activity and cumulative disease activity will be calculated, and categorised as absent, low, medium and high disease activity. At the time of their registration, patients have already consented to information form their medical file being disclosed to the BSRBR.

Sample sizes:
On 12/05/09 there were 49 patients, registered with the BSRBR, who had been treated with biologic drugs for RA and diagnosed with lymphoma during the study. This number will increase as patients continue to be followed in the register.
The study has 88% power to detect a 25% difference in the proportion of patients with high disease activity between 50 cases and 200 controls.

Time scale: It is estimated that it will take up to 2 months to reclassify lymphoma tissue blocks from 50 patients. It will take an estimated 12 months to review the casenotes of around 250 biologics treated patients, with and without lymphoma, in 40-50 hospitals to determine cumulative disease activity.

Additional work for the consultant / rheumatology specialist nurse entails retrieving case notes for the above patients.

Any other relevant information

Applicants may indicate any specific ethical issues relating to the amendment, on which the opinion of the REC is sought.
Whilst it is not mandatory to obtain consent to review material collected prior to September 1st 2006, we intend to obtain written consent from all patients that are still alive at the time of requesting the pathological specimen. However, in patients that are deceased it is impractical for us to seek consent from the next of kin since we do not record their contact details. Furthermore, we feel that it may be distressing to the next of kin to seek permission.
Written consent will be requested from patients as detailed below:

1. **Live patients:** For use of retrospectively archived material we propose sending a letter to the patient's Rheumatology consultant, which they will then copy onto their own headed paper and send to patients on our behalf endorsing their approval of the project (Appendix B). An information leaflet explaining the project in detail and a consent form will be enclosed (see Appendices D and E) of the study protocol). Patients will be invited to contact Dr Louise Mercer or Dr Kimme Hyrich at the BSRBR, and are also advised they may discuss the project with their Rheumatologist or Specialist

Nurse. Patients will be asked to give or withhold informed consent for use of their tissue on the enclosed consent form.

2. **Dead patients:** We do not wish to write to the relatives of dead patients for the following reasons:

    1. Request for written consent from relatives may provoke emotional distress, particularly if they were recently bereaved.
    2. Tests will be carried out on tumour tissue (not organs) previously removed at surgery for the purpose of patient assessment and management. This archived material is stored for future confirmation of diagnosis and comparison with secondary or other tumours that may develop; at completion of the proposed study, sufficient tissue will remain for this purpose.
    3. Patients will not be directly involved in the research.
    4. Tissue, including correlation of clinical and pathological findings, will be anonymised.
    5. The results of this research will not pose any risk of adverse effect on the patient or their relatives.
    6. We do not keep records of next of kin details.

The BSRBR includes the mortality status of patients. Where there is doubt, we will first contact the patient's consultant to establish whether the patient is still alive.

List of enclosed documents

Document	*Version*	*Date*
Appendix A: Letter to consultant	1	10th August 2009
Appendix B: Letter to patient	1	10th August 2009
Appendix C: Letter to Pathologist	1	10th August 2009
Appendix D: Patient information sheet	1	10th August 2009
Appendix E: Patient consent form	1	10th August 2009

Declaration

- I confirm that the information in this form is accurate to the best of my knowledge and I take full responsibility for it.
- I consider that it would be reasonable for the proposed amendment to be implemented.

Signature of Chief Investigator: ……

Print name:	……
Date of submission:	……..

Reference List

(1) Smitten AL, Simon TA, Hochberg MC, Suissa S. A meta-analysis of the incidence of malignancy in adult patients with rheumatoid arthritis.[see comment]. Arthritis Research & Therapy 2008;10(2):R45.

(2) Baecklund E, Iliadou A, Askling J, Ekbom A, Backlin C, Granath F, et al. Association of chronic inflammation, not its treatment, with increased lymphoma risk in rheumatoid arthritis.[see comment]. Arthritis & Rheumatism 2006 Mar;54(3):692-701.

(3) Maini R, St Clair EW, Breedveld F, Furst D, Kalden J, Weisman M, et al. Infliximab (chimeric anti-tumour necrosis factor alpha monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomised phase III trial. ATTRACT Study Group. Lancet 1999 Dec 4;354(9194):1932-9.

(4) Weinblatt ME, Keystone EC, Furst DE, Moreland LW, Weisman MH, Birbara CA, et al. Adalimumab, a fully human anti-tumor necrosis factor alpha monoclonal antibody, for the treatment of rheumatoid arthritis in patients taking concomitant methotrexate: the ARMADA trial.[see comment][erratum appears in Arthritis Rheum. 2003 Mar;48(3):855]. Arthritis & Rheumatism 2003 Jan;48(1):35-45.

(5) Klareskog L, van der Heijde D, de Jager JP, Gough A, Kalden J, Malaise M, et al. Therapeutic effect of the combination of etanercept and methotrexate compared with each treatment alone in patients with rheumatoid arthritis: double-blind randomised controlled trial. The Lancet 2004 Feb 28;363(9410):675-81.

(6) Balkwill F. Tumor necrosis factor or tumor promoting factor?. [Review] [89 refs]. Cytokine & Growth Factor Reviews 2002 Apr;13(2):135-41.

(7) Lienard D, Eggermont AM, Koops HS, Kroon B, Towse G, Hiemstra S, et al. Isolated limb perfusion with tumour necrosis factor-alpha and melphalan with or without interferon-gamma for the treatment of in-transit melanoma metastases: a multicentre randomized phase II study. Melanoma Research 1999 Oct;9(5):491-502.

(8) Eggermont AM, Schraffordt KH, Klausner JM, Kroon BB, Schlag PM, Lienard D, et al. Isolated limb perfusion with tumor necrosis factor and melphalan for limb salvage in 186 patients with locally advanced soft tissue extremity sarcomas. The cumulative multicenter European experience. Annals of Surgery 1996 May;224(6):756-64.