Staffordshire and NHS
Stoke on Trent Partnership
NHS Trust

Haywood Hospital
High Lane
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# FINAL STUDY REPORT

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| **Study Title:** | Efficacy Of Rituximab (Mabthera) in active ankylosing spondylitis: a clinical and magnetic resonance imaging study. |
| **REC Ref:** | 06/Q2604/39 |
| **EudraCT number:** | 2005-005358-27 |
| **Chief Investigator:** | Dr J Packham |
| **Sponsor:** | ~~Roche Pharmaceuticals~~ UNIVERSITY HOSPITALS OF NORTH MIDLANDS NHS TRUST. |

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| **Principal Investigator and Site** | Dr J Packham<br><br>Haywood Hospital, High Lane, Burslem Stoke on Trent |
| **Publications (or plans for publications)** | **BSR AGM 2008 - oral poster presentation:**<br>A pilot study of MRI response to Rituximab in AS<br><br>**New Perspectives in Research in Ankylosing Spondylitis (national AS meeting) 2008:**<br>Rituximab in AS<br><br>Abstract of paper submitted to 'Rheumatology' and 'AC&R'<br>Awaiting re-submission to J Rheumatology |
| **References to Support the Trial** | **Anderson JJ, Baron G, van der Heijde D, Felson DT, Dougados M.** Ankylosing spondylitis assessment group preliminary definition of short-term improvement in ankylosing spondylitis. Arthritis Rheum.2001 Aug;44(8): 1876-86. |

| References Continued | **Braun J, Pham T, Sieper J, Davis J, van der Linden S, Dougados M, van der Heidje D.** International ASAS consensus statement for the use of anti-tumour necrosis factor agents in patients with ankylosing spondylitis. Ann Rheum Dis 2003; 62 (9):817-24<br><br>**Braun J, Bollow M, Seyrekbasan F et al.** Computer tomography guided corticosteroid injection of the sacroiliac joint in patients with spondyloarthropathy with sacroiliitis: Clinical outcome and follow up by dynamic magnetic resonance imaging. J Rheumatol 1996;23,659-64<br><br>**Davis JC, van der Heijde D, Braun J et al.** Recombinant human tumour necrosis factor receptor (Etanercept) for treating Ankylosing Spondylitis. Arthritis Rheum 2003;48:11,3230-6<br><br>**Douagdos M, Gueuguen A, Nakache JP et al.** Clinical Relevance of C-Reactive Protein in Axial Involvement in Ankylosing Spondylitis. J Rheumatol 1999;26:4,971-4<br><br>**Edwards JCW, Cambridge G.** Do self - perpetuating B lymphocytes drive human autoimmune disease? Immunology 1999;97:188-96<br><br>**Edwards JC, Szezepanski L, Szechinski J et al.** Efficacy of B-cell targeted therapy with Rituximab in patients with rheumatoid arthritis. NEJM 2004 June; 350 (25): 2572-2581<br><br>**Van der Heijde D, Bellamy N, Calin A et al.** Preliminary Core Sets for Endpoints in Ankylosing Spondylitis. J Rheumatol 1997;24:11,2225-9<br><br>**Hickling P, Turnbull L, Dixon JS.** The Relationship Between Disease Activity, Immunoglobulins and Lymphocyte Sub-Populations in Ankylosing Spondylitis. Rheumatol and Rehab 1982 Aug:21(3),145-50<br><br>**Klareskog L, van der Heidje D, de Jager JP 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;363:675-681<br><br>**Ostergaard M, Klarlund M, Lassere M et al.** Inter-reader agreement in the assessment of magnetic resonance images of rheumatoid arthritis wrist and finger joints – an international multicenter study. J Rheumatol 2001;28:1143-50<br><br>**Maksymowych WP, Jhangri GS, Lambert RG et al.** Infliximab in Ankylosing Spondylitis: A Prospective Observational Inception Cohort Analysis of Efficacy and Safety. J Rheumatol 2002;29:5,959-65 |
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| **References Continued** | **Marzo-Ortega H, McGonagle D, O'Connor P et al.** Efficacy of Etanercept in the treatment of the entheseal pathology in resistant spondyloarthropathy. Arthritis Rheum 2001;44(9): 2112-2117<br><br>**Spoorenberg A, de Vlam K, va der Heidje D et al.** Radiological Scoring Methods In Ankylosing Spondylitis: Reliability and Sensitivity to Change Over One Year. J Rheumatol 1999;26:4,997-1002<br><br>**Tan AL, Marzo-Ortega H, O'Connor P et al.** Efficacy of anakinra in active ankylosing spondylitis: a clinical and magnetic resonance imaging study. Ann Rheum Dis Sept 2004; 63(9): 1041-1045<br><br>**Voswinkel J, Weisgerber K, Pfreundschuh M et al.** B Lymphocyte Involvement in Ankylosing Spondylitis: the Heavy Chain Variable Segment Gene Repertoire of B Lymphocytes from Germinal Center-like Foci in the Synovial Membrane Indicates Antigen Selection. Arthritis Research 2001:3 (3),189-95 |
| **Trial Start and End Date** | Start Date – 20th September 2006<br><br>End Date – 8th July 2009 |
| **Study Design** | Open label, prospective observational study of the efficacy and safety of mabthera (rituximab) in patients with ankylosing spondylitis (AS). |
| **Number of Patients** | 10 patients |
| **Inclusion/exclusion criteria** | **INCLUSION CRITERIA**<br><br>• Patients willing and able to give informed consent and to comply with the requirements of the protocol.<br>• Bath AS disease activity (basdai) index>4 (on a scale of 0-10)<br>• Nocturnal and total back pain visual analogue scale (0-100mm) over 40mm<br>• Acute inflammatory response (C reactive protein (CRP) > 10mg/L)<br>• Failure to respond to at least one non-steroidal anti-inflammatory drugs (NSAIDS)<br>• If the patient is of reproductive potential (males and females), then they must be using a reliable means of contraception (e.g. contraceptive pill, intrauterine device, physical barrier) |

**EXCLUSION CRITERIA**

- Contraindications to MRI
- Bone/joint surgery within 8 weeks prior to screening or joint surgery planned within 36 weeks trial entry
- Rheumatic disease other than AS
- Psoriasis
- Inflammatory bowel disease
- Current or previous anti-TNF
- Oral Predinisolone dose above 10mg daily
- Previous treatment will any cell depleting therapies, including investigational agents
- Previous treatment within 6 months with iv y-globulin or Prosorba Column
- Intra articular or parenteral corticosteroids within 4 weeks prior to screening visit or during the trial.
- History of severe allergic anaphylactic reactions to humanized or murine monoclonal antibodies.
- Significant cardiac or pulmonary disease.
- Known significant uncontrolled concurrent diseases such as renal, hepatic, nervous system, endocrine or gastrointestinal disorders.
- Known active bacterial, viral, fungal (excluding fungal infections of the nails bed), mycobacterial or other infections, or any major episode of infection requiring hospitalisation within 4 weeks of screening.
- History of significant recurrent infections.
- Primary or secondary immunodeficiency
- History of cancer. Including solid tumours and haematological malignancies (except basal cell and squamous cell carcinoma of the skin that have been excised and cured).
- Pregnant or lactating females.
- History of alcohol, drug or chemical abuse within 6 months of screening.
- Lack of peripheral venous access
- Intolerance or contraindications to oral or iv corticosteroids.
- Intolerance or contraindications to oral methotrexate.
- Serum crearinine > 140 umol/L
- Aspartate aminotransaminaise (AST) or alanine aminotransaminase (ALT) >2.5 times upper limit of normal.
- Platelet count < 100 $10^9$/L
- Haemoglobin <8.5 g/dL
- Neutrophils <1.5 x $10^3$/μL
- Levels of IgG and IgM below 5.65 and 0.55 mg/mL respectively.

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| **Investigational Medicinal Product** | Rituximab (MabThera)<br><br>Route of Administration - Intravenous infusion |
| **Treatment Duration** | 12 months |
| **Primary Objective/Outcome** | The primary objective was to determine the efficacy of Rituximab (MabThera), a B cell depleting chimeric monoclonal antibody in ankylosing spondylitis (AS).<br><br>The primary outcome of response to Mabthera treatment was the change in spinal and sacroiliac enthesitis/osteitis using magnetic resonance imaging (MRI) comparing the scores at 0 and 3 months. Patients were then followed up at 6 and 12 months with a further suppressed MRI of the sacroiliac joints and lumbar spine. |
| **Secondary Objectives/Outcomes** | The secondary outcome included changes before and after treatment in:<br>• Bath AS Disease Activity Index (BASDAI)<br>• Bath AS Functional Index (BASFI)<br>• Bath AS Metrology Index (BASAMI)<br>• SF-36<br>• ASQoL and ASQ (AS quality of life)<br>• 66 swollen joint count, MASES enthesitis score<br>• CRP/ESR and a broad screen of cytokines linked to AS disease activity including IL-1,IL-6, TNF-α,TGFβ1, VEGF, M-CRF, IFNγ and MMP-3<br>• VAS scores for patient global assessment, nocturnal back pain, total back pain |
| **Methodology** | A 12 month open label study of Rituximab (1000mg IV at 0 and 2 weeks) was carried out in 10 patients with active AS who had active disease (BASDAI>4), pain (pain VAS > 4/10), an increased acute phase response (C reactive protein (CRP)>10), and who had failed to respond to at least one non-steroidal anti-inflammatory drug. Clinical assessment included AS Quality of Life (ASQoL), general health status (SF-36), and the Bath AS measures of: Functional Index (BASFI), Disease Activity Index (BASDAI) and metrology (BASMI) before treatment and 3, 6, and 12 months after treatment. Fat suppressed MRI of the spine and sacroiliac joints was performed with a 1.5 T scanner at baseline, 3, 6 and 12 months to determine the effect of treatment on spinal enthesitis / osteitis. |

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| **Results** | There was a significant reduction in peripheral joint swelling (mean baseline 3.7, 6 months 2.5, p=0.044) and a borderline improvement in BASFI (mean baseline 7.7, 6 months 6.0, p=0.052, but no significant improvement of disease activity (BASDAI), quality of life (ASQoL/EASIQoL) or laboratory measures of (CRP and erythrocyte sedimentation rate (ESR)). Four patients (40%) achieved the Assessments in AS (ASAS) Working Group criteria of 20% improvement at 6 months.<br><br>Regions of MRI determined enthesitis / osteitis significantly reduced at the lumbar spine vertebrae (mean baseline 6.0, 6 months 2.9 $p<0.05$), lumbar spine pedicles (mean baseline 5.9, 6 months 3.3 $p<0.05$) and total lumbar and sacroiliac score (mean baseline 14.6, 6 months 7.9 $p<0.005$). None of the above improvements had achieved significance by 3 months and all had become non-significant 12 months after treatment |
| **Conclusion** | This open label pilot study suggests that Rituximab is likely to have an effect in reducing the MRI determined spinal enthesitis / osteitis and peripheral synovitis in AS. Other clinical manifestations of AS showed less objective evidence of improvement. |

Principal Investigator:

Signature:

Date: