Institution: University College London

Unit of Assessment: 4 - Psychology, Psychiatry and Neuroscience

Title of case study: Natalizumab: a potent treatment for highly active relapsing-remitting multiple sclerosis

1. Summary of the impact

Multiple Sclerosis (MS) is the most common disabling neurological disease of young adults in the UK, affecting 1 in 800 of the population. In most patients the early years are characterised by relapse and remissions; relapses are often disabling and permanent disability occurs when remissions fail to recover fully. Research at the UCL Institute of Neurology – from early MRI studies through phase 1-3 clinical trials – has resulted in the licensing of natalizumab for highly active relapsing remitting MS. Natalizumab is now widely used to treat such patients with very good efficacy and close monitoring. Natalizumab is a potent treatment that has reduced relapse rate by two-thirds and relapse-related disability by 50%. By July 2013, over 115,000 patients around the world had received this treatment.

2. Underpinning research

Serial magnetic resonance imaging (MRI) studies at the Institute of Neurology showed that blood-brain barrier (BBB) breakdown is a key early event in new lesion formation in relapsing remitting MS **[1]**, and the work of the Unit played a lead role in defining protocols for using MRI in proof-of concept trials of potential new disease modifying treatments **[2]**. The evidence for the important role of BBB leakage provided a rationale for investigating natalizumab, a monoclonal anti-adhesion molecule antibody that was shown to prevent trafficking of mononuclear white blood cells from blood to brain in an experimental model of MS.

Members of the Nuclear Magnetic Resonance (NMR) Unit, led by Professor David Miller, investigated the efficacy of natalizumab by performing central MRI analysis of multicentre Phase 1/2a and Phase 2b placebo-controlled trials in relapsing MS using MRI lesion activity as the primary outcome measure.

The phase 1/2a study was a UK-based, parallel-group, placebo-controlled trial in which Miller was the principal investigator. Study subjects received two doses of placebo or natalizumab one month apart and were followed up with regular MRI scans for six months. The study reached its primary end point: the adjusted mean cumulative number of new active lesions was lower after three months in the natalizumab-treated group than in the placebo group (1.8 vs 3.6; *P*=.04, analysis of covariance) **[3]**. In an accompanying editorial, the trial finding was described as a “near hit.” Had the study not reached its primary end point, one could speculate that it would have been a near miss and that the drug would not have been investigated further.

A subsequent phase 2b multicentre, multinational study was undertaken in patients with relapsing remitting MS or secondary progressive MS that tested placebo vs. natalizumab in two doses given intravenously every month for six months, followed by a six-month observation, and was robustly powered to detect an effect on MRI lesion activity. This study demonstrated profound (90%) suppression of new gadolinium-enhancing lesions during a six-month treatment phase. Although not powered to do so it showed a significant reduction in relapse rate in the natalizumab-treated arms. Magnetic resonance imaging activity returned to baseline levels during the six-month post-treatment observation period **[4]**.

Together with Dr Gavin Giovannoni (also UCL), Miller was leading investigator in the large phase 3, multicentre, placebo-controlled trial that followed, with Miller’s group providing central MRI analysis for the trial. This trial showed that natalizumab treatment was associated with a two-thirds reduction in relapse rate compared with placebo and a reduction in the accumulation of disability

by 50% **[5]**. It also reduced the rate of new lesion formation by ~90%.

The phase 3 trials of natalizumab did, however, identify a serious adverse effect: about one person in 1,000 developed progressive multifocal leucoencephalopathy (PML), a severe and sometimes fatal viral brain disease. Professor Tarek Yousry (Department of Brain Repair and Rehabilitation, UCL Institute of Neurology) led an international group that defined the risk for PML **[6]** and he and Miller have since contributed to subsequent guidelines for monitoring natalizumab-treated patients for early detection of PML. Risk counselling and monitoring for PML is an extremely important part of current treatment with natalizumab and is discussed in a recent review by Miller and Dr Jeremy Chataway (also UCL) **[7]**.

3. References to the research

[1] Miller DH, Barkhof F, Nauta JJP. Gadolinium enhancement increases the sensitivity of MRI in detecting disease activity in multiple sclerosis. Brain. 1993 Oct;116(Pt. 5):1077-94. http://dx.doi.org/10.1093/brain/116.5.1077

[2] Miller DH, Albert PS, Barkhof F, Francis G, Frank JA, Hodgkinson S, Lublin FD, Paty DW, Reingold SC, Simon JH. Guidelines for using magnetic resonance techniques in monitoring the treatment of multiple sclerosis. Annals of Neurology. 1996 Jan;39(1):6-16. http://www.ncbi.nlm.nih.gov/pubmed/8572668

[3] Tubridy N, Behan PO, Capildeo R, Chaudhuri A, Forbes R, Hawkins CP, Hughes RAC, Palace J, Sharrack B, Swingler R, Young C, Moseley IF, MacManus DG, Donoghue S, Miller DH, and the UK Antegren Study group. The effect of anti-alpha-4 integrin antibody on brain lesion activity in MS. Neurology. 1999 Aug;53(3):466-72. http://dx.doi.org/10.1212/WNL.53.3.466

[4] Miller DH, Khan OA, Sheremata WA, Blumhardt LD, Rice G, Libonati LA, Wilmer-Hulme A, Dalton C, Miszkiel K, O'Connor PW. A controlled trial of natalizumab for relapsing multiple sclerosis. N Engl J Med. 2003 Jan 2;348(1):15-23. http://dx.doi.org/10.1056/NEJMoa020696

[5] Polman CH, O'Connor PW, Havrdova E, Hutchinson M, Kappos L, Miller DH, Phillips JT, Lublin FD, Giovannoni G, Wajgt A, Toal M, Lynn F, Panzara MA, Sandrock AW; AFFIRM Investigators. A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. N Engl J Med. 2006 Mar 2;354(9):899-910. http://dx.doi.org/10.1056/NEJMoa044397

[6] Yousry TA, Major EO, Ryschkewitsch C, Fahle G, Fischer S, Hou J, Curfman B, Miszkiel K, Mueller-Lenke N, Sanchez E, Barkhof F, Radue EW, Jäger HR, Clifford DB. Evaluation of patients treated with natalizumab for progressive multifocal leukoencephalopathy. N Engl J Med. 2006 Mar 2;354(9):924-33. http://dx.doi.org/10.1056/NEJMoa054693

[7] Chataway J, Miller DH. Current status of natalizumab as a treatment for MS: Natalizumab therapy for multiple sclerosis. Neurotherapeutics. 2013 Jan;10(1):19-28. http://dx.doi.org/10.1007/s13311-012-0171-4

Peer-reviewed funding

The MS NMR Research Unit at UCL Institute of Neurology has received continuous peer-reviewed programme grant support since 1990 from the UK MS Society to support MR imaging research in MS. The Unit has also been supported during this time by peer-reviewed project, fellowship, PhD and other smaller grants from multiple bodies including the Wellcome Trust, Medical Research Council, UK National Institute for Health Research and US National MS Society. The funded research has underpinned the development of imaging protocols that are now routinely used to identify potential new disease-modifying treatments for MS.

4. Details of the impact

Multiple sclerosis (MS) is the most common disabling neurological disease of young adults in the UK, affecting 1 in 800 of the population. It is associated with high health care and socioeconomic costs and a markedly reduced quality of life. The first available disease-modifying treatments – beta interferon and glatiramer acetate – were introduced in the 1990s but proved to have only

limited effectiveness in preventing relapses and with only equivocal effects on related disability, and there remained a pressing need for more effective treatments. Furthermore, a NICE technology appraisal in 2002 found that these first-line treatments were not cost effective for use in the NHS and since then they have only been available to treat MS patients through a unique Department of Health Risk Sharing Scheme that was designed to ensure, through long term monitoring over ten years of a large patients cohort (2002-15), that cost effectiveness is achieved.

Following the pivotal phase 3 trial of natalizumab described above, a full UK National Institute of Health and Clinical Excellence (NICE) technology appraisal of natalizumab was undertaken in 2007. The outcome was that natalizumab became the first NICE-recommended disease-modifying treatment for MS available in the UK National Health Service. The drug was also approved by regulatory authorities for the treatment of active relapsing remitting MS in many countries around the world (see full details below).

Key impacts: benefits for MS patients

The following major clinical benefits of natalizumab for people with MS were identified in the phase 3 trial **[see 5, above]**:

1. Relapse rate was reduced by two thirds in natalizumab-treated compared to placebo-treated patients; in a subgroup of patients with highly active relapsing remitting MS (who had had at least two relapses in the prior 12 months), the reduction in relapse rate achieved by natalizumab was 81%; furthermore, natalizumab reduced the rate of hospitalisations by 64% and the need of steroid treatment for relapses by 69% **[a]**.
2. 50% fewer people treated with natalizumab developed a persistent increase in disability when compared with those treated with placebo. This reduction in disability accrual was even higher at 64% in the subgroup with highly active disease. Natalizumab is the first treatment for MS to show a large and unequivocal effect in preventing irreversible disability. A substantial number of natalizumab-treated patients actually experienced a reduction in their level of disability when compared with their status before entering the trial.
3. Clinically significant visual loss during the trial was reduced by 35% in natalizumab-treated patients compared to placebo, and overall visual function remained stable in natalizumab-treated patients whereas it deteriorated in placebo-treated subjects **[b]**
4. Health-related quality of life, which is often substantially impaired in people with MS, was significantly improved in patients treated with natalizumab **[c]**. The improvements were seen in both physical and mental components of quality of life measures.
5. Natalizumab also reduced the risk of a confirmed worsening of cognitive function by 43% compared with placebo **[a]**.

Licensing and prescription of natalizumab

Following the phase 3 clinical trials, natalizumab (trade name Tysabri) was granted regulatory approval in the United States (FDA, 2006) **[d]**, European Union (EMEA, 2006) **[e]**, Canada **[f]** and Australia **[g]**. It was recommended in 2007 by the UK National Institute for Health and Clinical Excellence as a clinically and cost effective treatment in the NHS for patients with rapidly evolving severe relapsing remitting MS **[h]**. The Medical Director (UK) at Biogen (the manufacturers of natalizumab) has confirmed that there is "*No doubt that the input from Dr Miller's research collaboration was an important contribution to the regulatory license application for Marketing approval by the relevant regulatory authorities*" **[i]**.

As a result of these approvals, natalizumab is now widely used to treat patients with highly active relapsing remitting MS. By December 2011, over 99,000 people worldwide had been treated with natalizumab **[j]**. Since that time, usage has continued to grow, with Biogen reporting sales of $1.6bn (an increase of 8%) for 2012 **[k]**. By July 2013, over 115,000 patients had been treated **[l]**.

As well as the direct financial benefits to Biogen in terms of sales, the licensing of natalizumab has resulted in increased employment and economic benefits in the US and Europe **[m]**.

Contribution to guidelines

Due to the rare complication of PML, natalizumab is largely used as a second-line treatment in highly active MS. Guidelines have been developed for treatment and monitoring of people who are treated with natalizumab and Yousry and Miller have contributed to these guidelines **[n]**. A key part of clinical monitoring of patients treated with natalizumab is to perform regular MRI scans looking for evidence of PML. Yousry has headed an international panel that has identified the radiological features typical of PML in natalizumab-treated patients; the panel has also recommended MRI protocols for monitoring patients **[o]**.

5. Sources to corroborate the impact

[a] Weinstock-Guttman B, Galetta SL, Giovannoni G et al. Additional efficacy endpoints from pivotal natalizumab trials in relapsing-remitting MS. J Neurol 2012;259:898-905. http://dx.doi.org/10.1007/s00415-011-6275-7

[b] Balcer LJ, Galetta SL, Calabresi PA et al. Natalizumab reduces visual loss in patients with relapsing multiple sclerosis. Neurology 2007;68:1299-304. http://dx.doi.org/10.1212/01.wnl.0000259521.14704.a8

[c] Rudick RA, Miller D, Hass S, et al.; AFFIRM and SENTINEL Investigators. Health-related quality of life in multiple sclerosis: effects of Natalizumab. Ann Neurol. 2007;62:335-46. http://dx.doi.org/10.1002/ana.21163

[d] FDA approval: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory#apphist

[e] EMEA approval: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000603/WC500044686.pdf

[f] Canadian approval: http://www.health.gov.on.ca/en/pro/programs/drugs/ced/pdf/tysabri2.pdf

[g] Australian approval: http://www.mssociety.org.au/documents/TreatmentsForMS-Tysabri-natalizumab.pdf

[h] NICE guidelines: http://www.nice.org.uk/nicemedia/live/11822/36136/36136.pdf

[i] Email from Biogen. Copy available on request.

[j] Data from drug company website: http://www.tysabri.com/treating-multiple-sclerosis.xml

[k] http://www.forbes.com/sites/matthewherper/2013/02/06/biogen-to-buy-elans-tysabri-rights-for-3-25-billion/ "*Last year (2012), Tysabri sales were $1.6 billion, up 8% from 2011.*"

[l] Chalkley JJ, Berger JR. Progressive multifocal leukoencephalopathy in multiple sclerosis. Curr Neurol Neurosci Rep. 2013 Dec;13(12):408. http://dx.doi.org/10.1007/s11910-013-0408-6.

[m] Kappos L, Bates D, Hartung HP, Havrdova E, **Miller D**, Polman CH, Ravnborg M, Hauser SL, Rudick RA, Weiner HL, O'Connor PW, King J, Radue EW, **Yousry T**, Major EO, Clifford DB. Natalizumab treatment for multiple sclerosis: recommendations for patient selection and monitoring. Lancet Neurol. 2007;6:431-41. http://dx.doi.org/10.1016/S1474-4422(11)70149-1

[n] **Yousry TA**, Pelletier D, Cadavid D, Gass A, Richert ND, Radue EW, Filippi M. Magnetic resonance imaging pattern in natalizumab-associated progressive multifocal leukoencephalopathy. Ann Neurol. 2012;72:779-87. http://dx.doi.org/10.1002/ana.23676

[o] http://www.mediconvalley.com/content/us3/news_events/latest_news/news_2011/news_q3_2011/biogen_idec_in_hillerod_to_hire_120_in_preparation_for_production_of_tysabri%C2%AE_for_non-us_market "*Biogen Idec's production facilities in Hillerød (Denmark) are preparing for production of TYSABRI® in 2013. The production facility, which is identical to and has the same production capacity as Biogen's facility in North Carolina, USA, will deliver to Biogen's market outside the USA. The present staff numbers about 180 and will be increased by 120 new employees ….*"