



Lessons for clinical trials from natalizumab in multiple sclerosis

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Drugs

Lessons for clinical trials from natalizumab in multiple sclerosis

Abhijit Chaudhuri

The approval of natalizumab and its recall after three months raises questions about the fast tracking of new drugs by the Food and Drug Administration for commercial licensing

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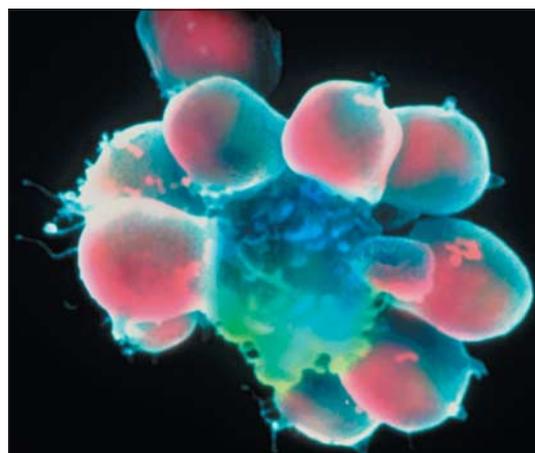
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On 28 February 2005 Biogen Idec and Elan voluntarily suspended marketing natalizumab (Tysabri or Antegren) for clinical use because two patients with multiple sclerosis developed progressive multifocal leucoencephalopathy (PML) while being treated. Clinicians were advised to suspend all ongoing trials, and commercial distribution of the drug was halted. Three months earlier the US Food and Drug Administration gave natalizumab accelerated approval to treat relapsing multiple sclerosis. Approval was given on the basis of short term (one year) data from two multi-centre, randomised double blind placebo controlled phase 3 trials. Neither trial was published in a peer reviewed journal and the FDA granted approval before final trial and cumulative safety data were available. PML has been confirmed in three patients taking natalizumab.¹⁻³

The unpublished multiple sclerosis trials

Natalizumab is a humanised monoclonal antibody to $\alpha 4$ integrin, which plays a key role in the adhesion and migration of immunocompetent T cells through its interaction with endothelial selective adhesion molecule.⁴ Approximately 3000 patients, mostly with multiple sclerosis and Crohn's disease, were treated with natalizumab in clinical trials, and nearly 5000 patients have been treated in the United States since it became commercially available in 2004. In the United Kingdom, natalizumab was due for appraisal by the National Institute for Health and Clinical Excellence in 2006 for use in multiple sclerosis.

In the two studies that formed the basis of its approval by the FDA, natalizumab was given intravenously every four weeks to patients with multiple sclerosis who had experienced at least one clinical relapse during the preceding year. The primary end point of each study was the annualised relapse rate at one year. In the first trial (the AFFIRM trial) patients were randomised 2:1 to receive natalizumab (n=627) or placebo (n=315). In the second study (the SENTINEL



T cell attacking a cluster of foreign red blood cells: natalizumab prevents the migration of immunocompetent T cells across biological barriers and suppresses T cell mediated immune responses

trial) patients had experienced at least one relapse, despite treatment with interferon beta-1a (Avonex; Biogen Idec). Patients were randomised to receive natalizumab (n=589) or placebo (n=582) in addition to intramuscular injections of interferon beta-1a. In the first study, patients receiving natalizumab had a relapse rate of 0.25 relapses per patient year, compared with 0.74 in the placebo group (66% relative reduction of relapses). In the second study, patients taking natalizumab had 0.36 relapses per patient year compared with 0.78 in the placebo group (54% relative reduction of relapses). The FDA concluded that natalizumab was superior to all available treatments for relapsing multiple sclerosis (three types of interferon beta and glatiramer).⁵

Safety data were available to the FDA for 1617 patients treated for multiple sclerosis in both controlled and uncontrolled studies.⁵ The median exposure time to the drug was 20 months and the most frequent serious adverse events were infection, hypersensitivity reactions, and depression.⁵

PML and natalizumab

On 18 February 2005, 10 days before the public announcement, the FDA received information from Biogen Idec of one confirmed death and one possible case of progressive multifocal leucoencephalopathy in patients receiving natalizumab for multiple sclerosis.⁶ There was a clear temporal association between treatment with natalizumab and the development of PML (box 1). As a selective blocker of adhesion molecules, natalizumab prevents the migration of immunocompetent T cells across biological barriers and suppresses T cell mediated immune responses. This therapeutic effect increases the risk of infections. PML is a rapidly progressive neurodegenerative disease usually caused by opportunistic infection with JC virus, a papova virus, and occasionally after simian virus 40 or BK polyoma virus infection in immunosuppressed patients.

The patient with Crohn's disease also received other immunosuppressive treatments (infliximab and azathioprine), both before and during the first phase of natalizumab infusion.¹ Both multiple sclerosis patients with confirmed PML were treated with interferon beta-1a before and during treatment with natalizumab.^{2,3} The use of other forms of immunotherapy may increase the risk of PML from natalizumab, and the risk may depend on the duration of treatment and the immunological status of the patient. The two reported cases of multiple sclerosis do not answer the important question of whether natalizumab had a therapeutic effect on the pathology of multiple sclerosis distinct from demyelination due to PML.

Approval of natalizumab and the FDA

Clinical trials are necessary to confirm the safety and efficacy of new treatments, but none of the published trials showed convincing evidence of the efficacy of natalizumab in relapsing multiple sclerosis.⁷ The first placebo controlled study where natalizumab (Antegren, Elan) was infused every two months showed no clinical effect.⁸ A study where natalizumab was infused every six months in patients with relapsing, remitting, and secondary progressive multiple sclerosis showed a 19% reduction in relapses but no benefit after treatment was stopped.⁹ A randomised, multicentre trial of natalizumab in acute relapses of multiple sclerosis found that treatment did not hasten recovery.¹⁰ Natalizumab had no proved effect on the progression of disability in these studies or in the two unpublished trials that formed the basis of its approval.⁵ The assumption that prolonged periods of monthly infusions of natalizumab are relatively safe is questionable, because few data are available from pre-clinical and clinical studies on the optimal duration of treatment and long term safety.

The approval of natalizumab and its recall after three months raises questions about the fast tracking of new drugs by the FDA for commercial licensing. It challenges the credibility of an evaluation process that allows accelerated approval of a product without full analysis of the trial data and adverse events. The optimal time for new drug approval has always been contentious,¹¹ but the regulatory authorities are expected to set out standards before treatments for life

long diseases are approved, especially when they target a younger population, as in multiple sclerosis. The FDA did not review the safety data of natalizumab in non-multiple sclerosis trials. The patient with Crohn's disease had died in 2003 from a serious adverse event related to treatment (initially diagnosed as malignant brain tumour) after receiving only eight doses of natalizumab.¹

Is natalizumab a viable treatment for multiple sclerosis?

Natalizumab was predicted to be the leading drug for multiple sclerosis, with estimated annual sales in excess of \$2bn (£1.2bn; €1.7bn), but the lack of safety data does not justify its long term clinical use. In a recent murine model of inflammatory colitis, long term treatment with anti- $\alpha 4$ integrin antibodies exacerbated the disease,¹² indicating that prolonged blockade of adhesion

Box 1: Summary of three patients developing progressive multifocal leucoencephalopathy after receiving natalizumab

Case 1

This 60 year old patient with long standing Crohn's disease presented with confusion and disorientation in July 2003.¹ He had been treated with natalizumab (eight infusions) since March 2002 in ENACT-1 and ENACT-2 trials (phase III trials of natalizumab in Crohn's disease). A brain biopsy was interpreted as astrocytoma. He died in December 2003, three months after treatment with corticosteroids. An autopsy was not performed. The brain biopsy was re-examined and the diagnosis revised to progressive multifocal leucoencephalopathy (PML). Retrospective analysis of serum samples detected JC virus in May 2003, and the viral load increased by a factor of 10 after two further injections of natalizumab, confirming a temporal relation between PML and natalizumab.

Case 2

The sensory and visual symptoms that developed at the age of 41 in this patient were attributed to multiple sclerosis,² although she had no oligoclonal bands in the cerebrospinal fluid. In January 2000 she had two new cortical (parietal) lesions on magnetic resonance imaging of the brain, and she began treatment with interferon beta-1a. She developed bladder dysfunction, paresthesia, spasticity, depression, and cognitive impairment. In April 2002 she was enrolled in the SENTINEL trial with an expanded disability status scale score of 0 (normal). She received natalizumab in combination with interferon beta-1a. Her disability scores remained stable between 0 and 2 (range 0 (normal) to 10 (death from multiple sclerosis)) until July 2004, but she did not develop deteriorating neurological symptoms due to PML until November 2004. Changes on imaging at this time were typical of PML. She died in February 2005 at the age of 46. She had received 37 monthly infusions of natalizumab. The diagnosis of widespread PML was confirmed at necropsy. She had no multiple sclerosis plaques, a finding that is not consistent with the diagnosis of multiple sclerosis. Microinfarction, rather than demyelination, was discovered in the parietal gyri and corpus callosum, which were not affected by PML.

Case 3

This patient presented in 1983 at the age of 23 with typical symptoms of multiple sclerosis and a family history of the disease. He averaged two to three relapses each year but had only mild ataxia. In 1998, he was started on interferon beta-1a. This reduced his relapse rate to one per year, but he had three exacerbations between 2001 and 2002 and was recruited to the SENTINEL trial.³ In November 2004 his doctors were alerted because of his inappropriate behaviour. Magnetic resonance imaging showed a large, new, frontal lesion on the right side of his brain and a biopsy revealed a diagnosis of PML. Natalizumab was withdrawn after 28 infusions. He responded to cytarabine (anti-metabolite chemotherapy effective against JC virus *in vitro*). Three months after stopping natalizumab he developed an inflammatory neurological syndrome associated with the clearance of JC virus after reconstitution of immunity, which supported the diagnosis of iatrogenic PML. He survived with severe motor and cognitive disabilities.

Box 2: Where now with natalizumab?

Natalizumab was developed on the basis of experimental allergic encephalomyelitis, which is not a reliable model of multiple sclerosis
 Preclinical safety data on dose and duration are limited
 It has not been shown to be effective as a treatment for relapse in acute multiple sclerosis
 No head to head trial with cyclical pulses of steroids (methylprednisolone) has been carried out
 Its therapeutic effect on the progression of disability in multiple sclerosis is not established
 The optimal duration of treatment is unknown
 The lifetime risk of progressive multifocal leucoencephalopathy after prolonged treatment (alone or in combination with other drugs) cannot be predicted
 Treatment with natalizumab is expensive, and no long term benefits have been proved

molecules prevents migration of lymphocytes, which is essential for viral immunosurveillance. By blocking T cell entry into the central nervous system, natalizumab may increase the risk of infections or viraemia, which may have adverse effects on patients with multiple sclerosis; as one author remarked, "bad things may happen when rescuers are turned back at the gates."¹³

In the unpublished trials, the claimed benefit of natalizumab was based on radiological measures (number of enhancing lesions in magnetic resonance images of the brain) and relapse rates, none of which correlate with long term disability in multiple sclerosis. Relapse rates are not continuous but discrete numbers, and fractional relapse rates are meaningless. Results of the AFFIRM trial indicate that without treatment (and associated risk of side effects) a patient would experience only one extra relapse in 16-18 months. Although the statistics of these trials may seem impressive, there is no half or three quarter relapse in a patient's life.

No trial compared monthly infusions of high dose corticosteroids with natalizumab. Pulse methylprednisolone improves short term recovery from relapse, has predictable side effects that can be minimised, and is much cheaper than natalizumab (annual cost of monthly natalizumab infusions \$23 500). The data for combination therapy (natalizumab and interferon beta-1a) were interesting: the annualised relapse rate for interferon beta-1a alone was slightly worse than for

placebo in the natalizumab monotherapy trial (0.78% and 0.74%),⁵ a result that questions the effectiveness of the drug.¹⁴

It is difficult to estimate the risk of PML in patients receiving natalizumab infusions over several years, but it is probably more than 1 in 1000. Even with prospective measurements of the JC viral load in plasma, natalizumab cannot be recommended in treated and previously untreated patients with multiple sclerosis because both its safety profile and efficacy data are short term. The use of natalizumab cannot be justified because the risk of PML is high and the long term efficacy of the drug is unknown (box 2).

Lessons from natalizumab trials

The experience with natalizumab shows that aggressive immunotherapy in multiple sclerosis to block T cell traffic in the central nervous system is risky and can be deadly. Multiple sclerosis is a chronic, lifelong disease and long term efficacy and safety data should be evaluated before new treatments are approved. The delayed and potentially fatal risks from mitoxantrone (cardiac failure and leukaemia), natalizumab (PML), and other aggressive forms of immunosuppression outweigh any marginal benefits in the short term. Reducing relapse is not necessarily an effective strategy to prevent serious and chronic disability in multiple sclerosis, as indicated by recent epidemiological models.^{15 16} The cost effectiveness of this treatment approach is also uncertain and has not been confirmed for interferon beta-1a, the most commonly prescribed disease modifying drug in multiple sclerosis.

The experience with natalizumab has also shown that clinical trials of new drugs put patients who volunteer at risk of consequences that may be fatal. Good clinical practice demands that all participants in clinical trials must be informed about "alternative procedure(s) or course(s) of treatment that may be available to the subject, and their important potential benefits and risks."¹⁷ Patients who volunteer for clinical trials should not be given the impression that they have the advantage of receiving new, potentially effective, safe, and free treatment. Patients should be made aware of the limitations of knowledge regarding adverse consequences and of the existing knowledge from previous clinical studies of similar treatments. Clinical investigators, who are the beneficiaries of sponsored drug trials and resulting publications, have a conflict of interest in recruiting patients. Independent institutional research groups could be set up to monitor the case selection and conduct of sponsored clinical trials for which institutions and researchers receive payment from industry.

We should be more careful about the diagnosis in patients who may not be "typical." Because the pathology did not support the clinical diagnosis of multiple sclerosis in the fatal case, the diagnosis is questionable,² and the decision to enrol an atypical patient (with an expanded disability status scale score of 0) is debatable. Magnetic resonance imaging of the spinal cord and visual evoked responses might have helped clarify the diagnosis. Clinicians should be cautious when diagnosing multiple sclerosis, especially when patients will be entered into clinical trials. Multiple sclerosis has no diagnostic laboratory marker, and appearances on

Summary points

Natalizumab was licensed for use in relapsing multiple sclerosis on the basis of short term results from two unpublished trials of treatment in Crohn's disease and multiple sclerosis

Three trial patients developed progressive multifocal leucoencephalopathy (incidence 1 in 1000) with a fatal outcome in two

The approval of natalizumab and its recall after three months raises questions about the fast tracking of new drugs for commercial licensing

Experience with natalizumab highlights the potential risks for patients in trials of new drugs where knowledge of long term efficacy, outcome measures, and safety is lacking

conventional brain scans are not specific for the disease. It is difficult to interpret enhancing lesions on magnetic resonance imaging in multiple sclerosis. Contrast enhancement in images indicates local breakdown of the blood-brain barrier, presumably owing to focal inflammation in multiple sclerosis, but contrast enhancement in the white matter after stress or hypoxia is due to inflammation. Surrogate markers based on imaging results used as outcome measures in multiple sclerosis trials do not mirror the clinical course of the disease. Although neurodegeneration is probably the most important cause of fixed and progressive disability in multiple sclerosis,¹⁸ imaging surrogates for neuroaxonal loss have not been validated for predicting future disability.¹⁹

Experimental allergic encephalomyelitis is not a suitable animal model for testing treatments for multiple sclerosis and it is time to explore alternative experimental and therapeutic approaches.¹⁴⁻²⁰ Clinical research is needed to reveal the biological variables that can distinguish relapsing progressive disease from relatively benign disease. A successful treatment should delay progressive tissue loss irrespective of relapse rates and clinical phenotype. Unusually for a neurological disease, the therapeutic time window for intervention is wide in multiple sclerosis, so that research on neuroprotective strategies should be a priority. Short term solutions for a chronic disease like multiple sclerosis are not likely to be effective, and PML resulting from treatment with natalizumab should be taken as a signal to change the way we treat this disease.

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Health policy

Have targets improved performance in the English NHS?

Gwyn Bevan, Christopher Hood

The star rating system for NHS trusts seems to have improved performance, but we still don't know how genuine the improvements are or the costs to other services

Annual performance ratings have been published for NHS trusts in England since 2001, and the fifth and final set was published in July 2005.¹⁻⁶ This process of naming and shaming gave each trust a rating from zero to three stars. Trusts that failed against a small number of key targets were at risk of being zero rated and their chief executives at risk of losing their job; trusts that performed well achieved three stars and were eligible for benefits from "earned autonomy."⁷ Although the government has abandoned the star ratings, targets are likely to remain. We consider reported improvements in performance against key targets, problems of the system, and what ought to happen in the future.

Reported improvements in performance

We compared data on performance in England before and after the star rating system for three key targets. When data were available we also compared English data with that of other UK countries that did not adopt the star system.

Accident and emergency departments

The key target for accident and emergency departments was the percentage of patients to be seen within four hours. From March 2003, the target was 90%,^{3 5}

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