

Natalizumab (Tysabri)

Fact Sheet

Multiple
Sclerosis
Trust

MS

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Natalizumab (Tysabri)

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1. Introduction

Natalizumab (brand name Tysabri) is a disease modifying drug licensed for use in people with highly active relapsing remitting multiple sclerosis including:

- people with highly active relapsing remitting MS who have failed to respond to treatment with beta interferon. Patients should have had at

least one relapse in the previous year whilst on therapy and have evidence of lesions on their MRI scan; or

- people with rapidly evolving severe relapsing remitting MS, defined as having two or more disabling relapses in one year and with evidence of increasing lesions on two consecutive MRI scans.

Studies have shown that natalizumab reduces the occurrence of relapses by around two thirds and significantly reduces the rate of disease progression. Treatment has been restricted to the listed groups due to safety concerns (see section 5).

2. How natalizumab works

Natalizumab is the first in a new class of drugs known as selective adhesion molecule (SAM) inhibitors.

In MS, it is believed that immune cells pass through the blood-brain barrier into the central nervous system (brain and spinal cord) where they can cause inflammation and potentially damage nerves and their surrounding myelin sheath. Adhesion molecules on the surface of immune cells play an important role in this process. Natalizumab binds to a specific adhesion molecule on the immune cell surface known as alpha-4 integrin and it is thought to act by preventing the cells from passing into the central nervous system via the blood-brain barrier.

3. Clinical trials of natalizumab

Two main studies have provided the evidence to support licensing of natalizumab for MS:

- The AFFIRM trial evaluated the effect of natalizumab on the progression of disability and the rate of clinical relapses.
- The SENTINEL trial evaluated the effect of the addition of natalizumab treatment in participants who were receiving interferon beta 1a (Avonex).

3.1. AFFIRM trial results

AFFIRM was a two-year, randomised, multi-centre, placebo-controlled, double-blind study of 942 people conducted in sites in America, Europe and Australasia. Participants received either a 300mg intravenous infusion dose of natalizumab or placebo every four weeks.

The two-year data showed that natalizumab reduced the rate of clinical relapses by 67% relative to placebo¹. The proportion of people who remained relapse free was 67% in the treatment group compared to 41% in the placebo group.

Natalizumab treatment also reduced the risk of progression of disability. After two years, 29% of placebo-treated patients had progressed, compared to 17% of natalizumab-treated patients. Progression was pre-defined as at least a one-point increase in the Expanded Disability Status Scale (EDSS) sustained for six months.

Benefits were also seen on the quality of life measures used in the study. A significant improvement was observed on both the physical wellbeing and mental wellbeing components of the Short Form-36 Health Survey (SF-36). General wellbeing also increased, as measured on a visual analogue scale.

3.2. SENTINEL trial results

SENTINEL was a two-year, randomised, multi-centre, placebo-controlled, double-blind study of 1,171 people taking interferon beta 1a who continued to experience disease activity. Participants received either natalizumab or placebo in addition to interferon beta 1a.

At two years, the addition of natalizumab to interferon beta 1a resulted in a 24% reduction in the risk of disability progression compared to the effect provided by interferon beta 1a plus placebo². The trial data also revealed a 56% reduction in the rate of clinical relapses in those receiving interferon beta 1a plus natalizumab compared with those receiving interferon beta 1a plus placebo. The reduction in relapse rate was statistically significant and sustained over the two-year period. Improvements in quality of life were also observed in this study.

Because of safety concerns (see section 5) the combination of natalizumab and other disease modifying treatments is not recommended.

4. How is natalizumab given?

Natalizumab is given as an intravenous infusion (a needle placed in a vein, similar to a drip) once every four weeks. It must be administered in a clinical setting under the supervision of a suitably qualified health professional.

5. Side effects and contraindications

5.1. Progressive multifocal leukoencephalopathy (PML)

The Food and Drug Administration (FDA), the body that regulates drugs in the USA, granted the first licence for natalizumab in November 2004. However, the drug was voluntarily withdrawn from the US market and European clinical trial programme only three months later. This followed reports of two cases, one fatal, of progressive multifocal leukoencephalopathy (PML) in patients who had received natalizumab in combination with Avonex as part of a two-year clinical trial.

PML is a rare brain infection caused by a virus called the JC virus. This virus is commonly found in the general population but only leads to PML if the immune system has been weakened, for example in transplant recipients or people with AIDS. In the case of natalizumab treatment, it is thought that PML develops because immune cells which would normally protect the brain from the JC virus are prevented from crossing the blood-brain barrier and entering brain tissue.

Like MS, PML causes damage to the protective sheath surrounding nerves in the central nervous system. It is a very aggressive condition for which there is no known effective treatment. Although not always fatal, it can cause death as little as one to six months after onset of symptoms. The symptoms of PML may be similar to those of an MS relapse.

In light of these incidents, the manufacturers initiated a safety review of all natalizumab clinical trial patients which identified a third case of PML in a patient who was taking part in a trial for Crohn's disease.

Following the completion of the safety evaluation³, the FDA authorised the return of natalizumab to the US market in June 2006 with restrictions imposed as to the groups of patients eligible for treatment. These restrictions are similar to those adopted in Europe.

Further cases of PML have been identified since natalizumab was licensed. A review of the first 28 cases observed that the risk of developing PML increases with the duration of treatment⁴. The review also summarised the clinical experience gained in diagnosing and managing these first cases of PML.

In January 2010 the European Medicines Agency (EMA) completed a review of natalizumab and the risk of PML. The EMA found that the risk of PML increases after two years of treatment although this risk remains low and the benefits of the drug continue to outweigh its risks for patients with highly active relapsing remitting MS⁵. The risk of developing PML was found to be equivalent to one case of PML for every 1,000 people treated with natalizumab for two years or more. They recommended a number of measures to ensure that those taking natalizumab and doctors are fully aware of the risks of PML. These include:

- label changes which aim to ensure that people taking the drug are fully aware of the risks and also offer additional advice on how to manage people who show signs of PML;
- updates to prescribing information to draw attention to the increase in the risk of PML after two years; and
- requiring people to sign a consent form when they start taking natalizumab and again after two years of treatment.

A risk-benefit analysis of natalizumab that modelled the long-term risks and benefits of the therapy in individuals with relapsing remitting MS, concluded that the benefit of long-term treatment with natalizumab far outweighed the risk of developing PML. A more than seven-fold increase in the risk of PML (ie an increase in risk from 1 in 1000 people treated to 7 in 1000) was required to decrease natalizumab's health gain below that of interferon beta 1a⁶.

If you are considering starting or continuing treatment with natalizumab, you should be given the opportunity to discuss the risks and benefits with your neurologist or MS nurse. They will be able to put the risk of PML into the context of how MS is affecting you personally and help you to make a decision about your treatment choices.

5.2. Natalizumab and potential risk of liver injury

Following regulatory review of the drug, a liver damage warning was added to the prescribing information for natalizumab. People receiving natalizumab therapy need to be made aware of the potentially increased risk of liver damage while health professionals are urged to be vigilant in monitoring for liver function abnormalities. Liver function generally recovers when therapy is stopped.

5.3. Other potential side effects

Commonly reported side effects of natalizumab include dizziness, nausea, urticaria (a skin rash) and stiffness. Natalizumab may increase chances of getting an unusual or serious infection.

6. Further information

Reports of earlier stages of research on natalizumab and MS are also available.

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