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EMA confirms recommendations to minimise risk of brain infection PML with Tysabri

More frequent MRI scans should be considered for patients at higher risk

The European Medicines Agency (EMA) has completed its review of the known risk of progressive multifocal leukoencephalopathy (PML) with the multiple sclerosis medicine Tysabri (natalizumab), and has confirmed initial recommendations[1] aimed at minimising this risk.

PML is a rare brain infection caused by John Cunningham (JC) virus. This virus is very common in the general population and is normally harmless; however, it can lead to PML in persons whose immune system is weakened. The most common symptoms of PML are progressive weakness, speech and communication difficulties, vision changes, and sometimes changes in mood or behaviour. PML is a very serious condition that may result in severe disability or death.

Recent studies suggest that early detection and treatment of PML when the disease is asymptomatic (is still in the initial stages and shows no symptoms) may improve patients' outcomes. Asymptomatic cases of PML can be detected on MRI scans, and experts in the field of MRI and multiple sclerosis agree that simplified MRI protocols (which allow for shorter procedures, and also limit the burden for patients undergoing the scans) permit the identification of PML lesions. All patients taking Tysabri should undergo full MRI scans at least once a year, but on the basis of the new data EMA now recommends that for patients at higher risk of PML more frequent MRI scans (e.g. every 3 to 6 months) performed using simplified protocols should be considered. If lesions suggestive of PML are discovered, the MRI protocol should be extended to include 'contrast-enhanced T1-weighted MRI', and testing the spinal fluid for the presence of JC virus should be considered.

New data from large clinical studies also suggest that, in patients who have not been treated with immunosuppressants (medicines that reduce the activity of the immune system) before starting Tysabri, the blood level of antibodies against JC virus ('antibody index') relates to the level of risk for PML. In light of the new evidence, patients are considered at higher risk of developing PML if they:

- have tested positive for JC virus, and
- have been treated with Tysabri for more than 2 years, and
- either have used an immunosuppressant before starting Tysabri, or have not used immunosuppressants and have a high JC virus antibody index.

[1] PRAC recommendations issued on 11 February 2016

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In these patients, treatment with Tysabri should only be continued if benefits outweigh the risks.

If PML is suspected at any time, treatment with Tysabri must be stopped until PML has been excluded.

EMA's recommendations are based on an initial review by its Pharmacovigilance Risk Assessment Committee (PRAC). The PRAC recommendations were sent to the Committee for Medicinal Products for Human Use (CHMP), which has now confirmed them and issued its final opinion. The CHMP's opinion will now be sent to the European Commission for a legally-binding decision valid throughout the EU.

Information for patients

- Progressive multifocal leukoencephalopathy (PML, a serious brain infection) is known to be an uncommon risk with the multiple sclerosis medicine Tysabri. New recommendations have been issued which may help early detection of PML and improve patients' outcomes.
- Your risk of PML depends on several factors, such as whether you have antibodies against JC virus in your blood (a sign that you have been exposed to the virus that causes PML) and what their level is, how long you have been treated with Tysabri, and whether or not you were treated with medicines that suppress your immune system before starting Tysabri. Considering these factors, your doctor will be able to advise you about your risk of developing PML.
- Before starting treatment with Tysabri, and then regularly during treatment, your doctor will do blood tests to measure the level of antibodies for JC virus and MRI scans to monitor your condition. Your doctor will also check for signs and symptoms suggestive of PML. These tests may be done more often if you are considered at higher risk for PML.
- If PML is suspected, your doctor will stop treatment with Tysabri until PML can be ruled out.
- Symptoms of PML may be similar to those of a multiple sclerosis attack, and include progressive weakness, speech and communication difficulties, vision problems, and sometimes changes in mood or behaviour. If you believe your disease is getting worse or if you notice any new or unusual symptoms while using Tysabri and for up to 6 months after stopping Tysabri, speak to your doctor as soon as possible.
- More information about the risk of PML with Tysabri is included in the Patient Alert Card you have been given by your doctor. It is important that you read this card carefully. Keep this card with you and make sure your partner or carer is aware of its content.
- If you have any questions or concerns, speak to your doctor, nurse or pharmacist.

Information for healthcare professionals

Known risk factors for the development of PML in patients treated with Tysabri are the presence of antibodies against JC virus, treatment with Tysabri for more than two years, and previous use of immunosuppressants. Pooled data from large clinical studies suggest that, in patients with no prior immunosuppressant use, the level of anti-JC virus antibody response (index) relates to the level of risk for PML. Based on these data, updated risk estimates for PML[2] in JC virus antibody-positive patients treated with Tysabri are available, as shown in Table 1 below:

[2] PML risk estimates were derived using the life table method based on the pooled cohort of 21,696 patients who participated in the STRATIFY-2, TOP, TYGRIS, and STRATA clinical studies. Further stratification of PML risk by anti-JC virus antibody index interval for patients with no prior use of immunosuppressants were derived from combining the overall yearly risk with the antibody index distribution.

Table 1: PML risk estimates per 1,000 patients in anti-JC virus antibody positive patients*

Duration of Tysabri use	No prior use of immunosuppressants				Prior use of immunosuppressants
	No index value	Index 0.9 or less	Index 0.9 to 1.5	Index more than 1.5	
1-12 months	0.1	0.1	0.1	0.2	0.3
13-24 months	0.6	0.1	0.3	0.9	0.4
25-36 months	2	0.2	0.8	3	4
37-48 months	4	0.4	2	7	8
49-60 months	5	0.5	2	8	8
61-72 months	6	0.6	3	10	6

*from Tysabri Physician Information and Management Guidelines

The updated risk estimates above show that the risk of developing PML is small, and lower than previously estimated, at antibody index values of 0.9 or less, and increases substantially in patients with index values above 1.5 who have been treated with Tysabri for longer than 2 years. In patients who tested negative for JC virus antibodies, the PML risk estimate remains unchanged at 0.1 per 1,000 patients.

More detailed information on the risk stratification, diagnosis and treatment of PML will be included in the updated Physician Information and Management Guidelines for Tysabri.

Healthcare professionals should follow these recommendations:

- Before starting treatment with Tysabri, patients and carers should be advised about the risk of PML. Patients should be instructed to seek medical advice if they think their disease is getting worse, or if they notice any new or unusual symptoms.
- Before starting treatment, a baseline MRI should be available (usually within 3 months) as a reference, and a baseline anti-JCV antibody test should be performed to support PML risk stratification.
- During treatment with Tysabri, patients should be monitored at regular intervals for signs and symptoms of new neurological dysfunction, and a full brain MRI should be performed at least once a year for the duration of treatment.
- For patients at higher risk of PML, more frequent MRIs (e.g. every 3-6 months) using an abbreviated protocol (e.g. FLAIR, T2-weighted and DW imaging) should be considered, as earlier detection of PML in asymptomatic patients is associated with improved PML outcomes.

- PML should be considered in the differential diagnosis of any patient presenting with neurological symptoms and/or new brain lesions on MRI. Cases of asymptomatic PML based on MRI and positive JC virus DNA in the CSF have been reported.
- If PML is suspected, the MRI protocol should be extended to include contrast-enhanced T1-weighted imaging and testing of CSF for the presence of JC virus DNA using ultrasensitive PCR should be considered.
- If PML is suspected at any time, treatment with Tysabri must be stopped until PML has been excluded.
- Anti-JC virus antibody testing should be done every 6 months in antibody-negative patients. Patients who have low index values and no history of prior immunosuppressant use should also be retested every 6 months once they reach the 2-year treatment point.
- After 2 years of treatment, patients should be informed again about the risk of PML with Tysabri.
- Patients and carers should be advised to continue to be vigilant about the risk of PML for up to 6 months following discontinuation of Tysabri.

More about the medicine

Tysabri is a medicine used to treat adults with highly active multiple sclerosis (MS), a disease of the nerves in which inflammation destroys the protective sheath surrounding the nerve cells. Tysabri is used in the type of MS known as 'relapsing-remitting' MS, when the patient has attacks (relapses) in between periods with no symptoms (remissions). It is used when the disease has failed to respond to treatment with a beta-interferon or glatiramer acetate (other types of medicines used in MS), or is severe and getting worse rapidly.

The active substance in Tysabri, natalizumab, is a monoclonal antibody (a type of protein) that has been designed to recognise and attach to a specific part of a protein called 'α4β1 integrin'. This protein is found on the surface of most leucocytes (the white cells in the blood that are involved in the inflammation process). By attaching to the integrin, natalizumab stops the leucocytes from going from the blood into the brain, thereby reducing the inflammation and nerve damage caused by MS.

Tysabri was authorised in the European Union in June 2006.

More about the procedure

The review of Tysabri was initiated on 7 May 2015 at the request of the European Commission, under Article 20 of Regulation (EC) No 726/2004.

The review was first carried out by the Pharmacovigilance Risk Assessment Committee (PRAC), the Committee responsible for the evaluation of safety issues for human medicines, which made a set of recommendations. The PRAC recommendations were then sent to the Committee for Medicinal Products for Human Use (CHMP), responsible for questions concerning medicines for human use, which adopted the Agency's final opinion.

The CHMP opinion will now be forwarded to the European Commission, which will issue a final legally binding decision applicable in all EU Member States in due course.

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