Feb 2010

Direct Healthcare Professional Communication: An update on the association of natalizumab (TYSABRI) with Progressive Multifocal Leukoencephalopathy (PML)

Summary

In patients with Multiple sclerosis (MS) receiving natalizumab (TYSABRI) 31 cases of Progressive Multifocal Leukoencephalopathy (PML) from approximately 66,000 people exposed have been reported until the 20th of January 2010.

The risk of developing PML appears to increase with duration of treatment. Out of 31 confirmed cases, reported to date, 23 occurred in patients exposed to TYSABRI for 2 years or more. The risk for developing PML beyond 3 years of treatment with TYSABRI is currently unknown.

The cases underline the importance of:

- informing patients about the risk of PML via a new treatment /continuation information form
- carefully reconsidering the benefit and risk of the treatment after 2 years together with the patient
- performing a Magnetic Resonance Image (MRI) within 3 months before initiation of treatment with TYSABRI, and repeating it on a yearly basis to update this reference
- continued clinical vigilance
- prompt discontinuation of TYSABRI when PML is suspected with subsequent appropriate evaluation, including a standardized magnetic resonance imaging (MRI) scan and lumbar puncture.
- preferably treating patients as part of national registries or post-marketing studies

Further information on the safety concern

Progressive Multifocal Leukoencephalopathy (PML) is a rare, progressive and demyelinating disease of the central nervous system that usually leads to death or severe disability. PML is caused by activation of JC virus, a polyoma virus that resides in latent form in the majority of healthy adults. JC virus usually remains latent, typically only causing PML in immunocompromised patients. The factors leading to activation of the latent infection are not fully understood.

The incidence of PML appears to increase with TYSABRI treatment duration, particularly after 2 years. In cases of PML seen to date, duration of exposure has ranged from

Biogen Idec (Ireland) Limited
United Drug House, Magna Drive, Magna Business Park, Citywest Road, Dublin 24, Ireland +353 (0) 1 463 7725
Fax +353 (0) 1 481 1730
Company Registration Number 421718

approximately 12 to 44 doses with the majority of the cases occurring in patients treated for greater than two years.

Further information on recommendations to healthcare professionals:
If a patient develops PML, TYSABRI must be permanently discontinued.

TYSABRI must be prescribed in compliance with the SmPC and according to the Physician Information and Management Guidelines.

Patients must be monitored at regular intervals for any new or worsening neurological symptoms or signs that may be suggestive of PML (such as impaired cognition, visual disturbances, hemiparesis, altered mental state or behavioural changes). If PML is suspected, further dosing must be suspended until PML has been excluded.

The clinician should evaluate the patient to determine if the symptoms are indicative of neurological dysfunction and, if so, whether these symptoms are possibly suggestive of PML. If any doubt exists, further evaluation, including Magnetic Resonance Imaging (MRI) scan preferably with contrast, cerebrospinal fluid (CSF) testing for JC viral DNA and repeat neurological assessment, should be considered.

Plasma exchange/immunoadsorption (PLEX/IA) has often been used to reduce the levels of TYSABRI more quickly when PML has been identified. The impact of plasma exchange on the restitution of lymphocyte migration and ultimately its clinical usefulness is unknown.

The use of PLEX/IA accelerates the development of IRIS, immune reconstitution inflammatory syndrome, in the following days to weeks. IRIS is probably an enhanced viral clearance by the immune system and can lead to a severe pathology. Monitoring for development of IRIS and appropriate treatment of the associated inflammation during recovery from PML should be undertaken.

Treatment could be started with a high dose systemic steroid at the first signs of IRIS. Patients with signs and symptoms suggestive of IRIS should receive intensive care monitoring. Prophylactic steroid treatment is currently not recommended, as it is unknown if prophylactic steroids could hinder clearance of JC virus from PML lesions and thus adversely impact recovery from PML. More information will be available in the updated Physician Information and Management Guidelines.

Patients should also be advised to inform their partner or caregivers about their treatment, since they may notice symptoms that the patient is not aware of.

The content of this letter has been agreed with the European Medicines Agency and the Irish Medicines Board.

Call for reporting

Please remember that any suspect adverse reaction following the use of TYSABRI should be reported.

Please remember that any suspect adverse event following the use of TYSABRI should be reported to the marketing authorisation holder at 1800 409 676 or to the Irish Medicines Board, in the usual way (using the yellow card system or online at www.imb.ie).

Communication information
For further information please contact: Medical Information 1800 812 719.

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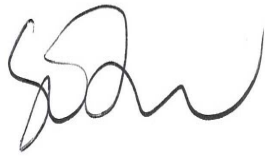
United Drug House, Magna Drive, Magna Business Park, Citywest Road, Dublin 24, Ireland +353 (0) 1 463 7725
Fax +353 (0) 1 481 1730
Company Registration Number 421718

Yours faithfully

Dr Grainne Quinn
Elan

Dr Glyn Belcher
Biogen Idec



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