

Understanding PML for Gastroenterologists


TYSABRI[®]
(natalizumab)

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The following information should be considered when undertaking the assessment and management of progressive multifocal leukoencephalopathy (PML) in adult patients treated with TYSABRI for moderately to severely active Crohn's disease (CD). During clinical trials for TYSABRI, 3 cases of PML were identified (2 in multiple sclerosis and 1 in Crohn's disease). Both multiple sclerosis patients were receiving concomitant immunomodulatory therapy and the Crohn's disease patient had been treated in the past with immunosuppressive therapy. In the postmarketing setting, additional cases of PML have been reported in multiple sclerosis and Crohn's disease patients who were receiving no concomitant immunomodulatory therapy.¹

About PML

PML is a demyelinating disease that attacks the central nervous system.² It is an opportunistic infection caused by the JC virus that typically occurs in patients who are immunocompromised.¹ The virus removes myelin that surrounds the nerves, and without this protection the nerves cannot transmit signals.³ There are no known interventions that can reliably prevent PML or adequately treat PML if it occurs.¹

How to Recognize PML

Typical symptoms associated with PML are diverse, progress over days to weeks, and include^{3,4}:

- Progressive weakness on one side of the body or clumsiness of limbs
- Disturbance of vision
- Changes in thinking, memory, and orientation, leading to confusion and personality changes
- Seizures

The progression of deficits usually leads to death or severe disability over weeks or months.³ Since these symptoms are very different from those of Crohn's disease, the appearance of any symptom of PML, including those listed above, should be investigated immediately.⁴ In Crohn's disease patients, a baseline brain MRI may also be helpful to distinguish pre-existent lesions from newly developed lesions, but brain lesions at baseline that could cause diagnostic difficulty while on TYSABRI therapy are uncommon.¹

This information is provided as an educational resource for healthcare providers and should be considered current as of the date listed herein. It is not intended to be a substitute for consultation and review of reference materials and medical literature pertaining to individual clinical circumstances. Healthcare providers should make all treatment decisions based on the context of the situation and their own clinical judgment.



Action Steps if PML Is Suspected

- TYSABRI dosing should be suspended immediately in all cases in which PML is suspected¹
- Immediate referral to a neurologist for assessment, potentially including¹:
 - A brain MRI to determine if lesions that could be due to PML are present
 - Cerebrospinal fluid evaluation for the presence of JCV DNA
- Potential cases of PML should be reported immediately to Biogen Idec or Elan at 1-800-456-2255, or to the FDA's MedWatch reporting system at 1-800-FDA-1088, or via the MedWatch Web site at www.fda.gov/medwatch

Note: TYSABRI dosing should be restored only if the diagnosis of PML is excluded and if deemed appropriate for the ongoing treatment of CD in patients with moderately to severely active Crohn's disease with evidence of inflammation who have had an inadequate response to, or are unable to tolerate, conventional CD therapies and inhibitors of TNF- α , and who are not taking concomitant immunosuppressants (e.g., 6-mercaptopurine, azathioprine, or methotrexate) or concomitant inhibitors of TNF- α .

Indication

TYSABRI is indicated for inducing and maintaining clinical response and remission in adult patients with moderately to severely active Crohn's disease with evidence of inflammation who have had an inadequate response to, or are unable to tolerate, conventional CD therapies and inhibitors of TNF- α . TYSABRI should not be used in combination with immunosuppressants (e.g., 6-mercaptopurine, azathioprine, cyclosporine, or methotrexate) or inhibitors of TNF- α .

Important Safety Information

WARNING

TYSABRI increases the risk of PML, an opportunistic viral infection of the brain that usually leads to death or severe disability. Cases of PML have been reported in patients taking TYSABRI who were recently or concomitantly treated with immunomodulators or immunosuppressants, as well as in patients receiving TYSABRI as monotherapy. Longer treatment duration, prior immunosuppressant use (e.g., mitoxantrone, azathioprine, methotrexate, cyclophosphamide, mycophenolate mofetil), and the presence of anti-JCV antibodies are three factors identified thus far that increase the risk of PML in TYSABRI-treated patients. The risks and benefits of continuing treatment with TYSABRI should be carefully considered in patient who are found to be anti-JCV antibody positive and have one or more additional risk factors. Healthcare professionals should monitor patients on TYSABRI for any new sign or symptom that may be suggestive of PML. TYSABRI dosing should be withheld immediately at the first sign or symptom suggestive of PML.

Important Safety Information Continued on next page



Important Safety Information (continued)

Hypersensitivity—TYSABRI has been associated with hypersensitivity reactions, including serious systemic reactions (e.g., anaphylaxis) which occurred at an incidence of <1%. If a hypersensitivity reaction occurs, administration of TYSABRI should be discontinued and appropriate therapy initiated.

Immunosuppression/Infection—The immune system effects of TYSABRI alone may increase the risk for infections. Concurrent use of antineoplastics, immunosuppressants, or immunomodulators may further increase the risk of infections, including PML and other opportunistic infections, over the risk observed with use of TYSABRI alone.

Hepatotoxicity—Clinically significant liver injury has been reported in some patients treated with TYSABRI in the postmarketing setting. TYSABRI should be discontinued in patients with jaundice or other evidence of significant liver injury (e.g., laboratory evidence). The combination of transaminase elevations and elevated bilirubin without evidence of obstruction is generally recognized as an important predictor of severe liver injury that may lead to death or the need for a liver transplant in some patients.

Adverse reactions—The most serious adverse reactions in TYSABRI clinical trials were opportunistic infections including PML, hypersensitivity, and immunosuppression/infections. The most common adverse reactions reported in CD studies were headache, fatigue, upper respiratory infections, and nausea.

References:

1. TYSABRI [prescribing information]. South San Francisco, CA: Elan Pharmaceuticals, Inc.; 2010. 2. Yousry TA, Major EO, Ryschkewitsch C, et al. Evaluation of patients treated with natalizumab for progressive multifocal leukoencephalopathy. *N Engl J Med*. 2006;354:924-933. 3. Data on file. South San Francisco, CA: Elan Pharmaceuticals, Inc. 4. Project Inform. Progressive multifocal leukoencephalopathy (PML). Available at: <http://www.projectinform.org/info/pml/index.shtml>. Accessed February 14, 2008.

Please see accompanying full Prescribing Information, including Boxed Warning.



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