

Understanding PML for Gastroenterologists

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.



Understanding PML for Gastroenterologists

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



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 at 1-800-456-2255, or to the FDA's MedWatch reporting system at 1-800-FDA-1088, or via the MedWatch website 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: Progressive Multifocal Leukoencephalopathy (PML)

TYSABRI (natalizumab) increases the risk of PML, an opportunistic viral infection of the brain that usually leads to death or severe disability. Risk factors for the development of PML include the presence of anti-JCV antibodies, duration of therapy, and prior use of immunosuppressants. These factors should be considered in the context of expected benefit when initiating and continuing treatment with TYSABRI.

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. For diagnosis, an evaluation including a gadolinium-enhanced MRI scan of the brain and, when indicated, cerebrospinal fluid analysis for JC viral DNA are recommended.

Because of the risk of PML, TYSABRI is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the TOUCH Prescribing Program.

Important Safety Information continued on next page.



Important Safety Information (continued)

Progressive Multifocal Leukoencephalopathy (PML)

- Infection by the JC Virus (JCV) is required for the development of PML.
- Anti-JCV antibody testing should not be used to diagnose PML.
- After plasma exchange (PLEX), wait at least two weeks to test for anti-JCV antibodies to avoid false negative test results caused by the removal of serum antibodies. After infusion of intravenous immunoglobulin (IVIg), wait at least 6 months (5 half-lives) for the IVIg to clear in order to avoid false positive anti-JCV antibody test results.
- There are no known interventions that can reliably prevent PML or that can adequately treat PML if it occurs. It is not known whether early detection of PML and discontinuation of TYSABRI will mitigate the disease.
- MRI findings may be apparent before clinical signs or symptoms suggestive of PML. Periodic monitoring for radiographic signs consistent with PML should be considered to allow for an early diagnosis of PML. Consider monitoring patients at high risk for PML more frequently. Lower PML-related mortality and morbidity have been reported following TYSABRI discontinuation in patients with PML who were initially asymptomatic compared to patients with PML who had characteristic clinical signs and symptoms at diagnosis.
- PML has been reported after discontinuation of TYSABRI in patients who did not have findings suggestive of PML at the time of discontinuation. Patients should continue to be monitored for any new signs or symptoms that may be suggestive of PML for approximately 6 months after discontinuation of TYSABRI.
- In MS patients, an MRI scan should be obtained prior to initiating therapy with TYSABRI. This MRI may be helpful in differentiating subsequent multiple sclerosis symptoms from PML.
- Three sessions of PLEX over 5 to 8 days were shown to accelerate TYSABRI clearance in a study of 12 patients with MS who did not have PML, although in the majority of patients, alpha-4 integrin receptor binding remained high. Adverse events that may occur during PLEX include clearance of other medications and volume shifts, which have the potential to lead to hypotension or pulmonary edema. Although PLEX has not been prospectively studied in TYSABRI-treated patients with PML, it has been used in such patients in the postmarketing setting to remove TYSABRI more quickly from the circulation. There is no evidence that PLEX has any benefit in the treatment of opportunistic infections such as PML.
- JCV infection of granule cell neurons in the cerebellum, i.e., JCV granule cell neuronopathy (GCN), with symptoms similar to PML, has been reported in patients treated with TYSABRI. JCV GCN can occur with or without concomitant PML and can cause cerebellar dysfunction. Diagnosis and management of JCV GCN should follow guidance provided for PML.
- Immune reconstitution inflammatory syndrome (IRIS) has been reported in the majority of TYSABRI treated patients who developed PML and subsequently discontinued TYSABRI. In almost all cases, IRIS occurred after plasma exchange was used to eliminate circulating TYSABRI. It presents as a clinical decline in the patient's condition after TYSABRI removal (and in some cases after apparent clinical improvement) that may be rapid, can lead to serious neurological complications or death and is often associated with characteristic changes in the MRI. TYSABRI has not been associated with IRIS in patients discontinuing treatment with TYSABRI for reasons unrelated to PML. In TYSABRI-treated patients with PML, IRIS has been reported within days to several weeks after plasma exchange. Monitoring for development of IRIS and appropriate treatment of the associated inflammation should be undertaken.

Important Safety Information continued on next page.



Contraindications

- TYSABRI is contraindicated in patients who have or have had PML.
- TYSABRI is contraindicated in patients who have had a hypersensitivity reaction to TYSABRI.

TYSABRI TOUCH Prescribing Program

- TYSABRI is available only through a restricted program under a REMS called the TOUCH® Prescribing Program because of the risk of PML.
- For prescribers and patients, the TOUCH® Prescribing Program has two components: MS TOUCH® (for patients with multiple sclerosis) and CD TOUCH® (for patients with Crohn's disease).
- Prescribers must be certified and comply with the following:
 - Review the TOUCH Prescribing Program prescriber educational materials, including the prescribing information.
 - Review, complete, and sign the Prescriber Enrollment Form.
 - Educate patients on the benefits and risks of treatment with TYSABRI, ensure that patients receive the Medication Guide, and encourage them to ask questions.
 - Review, complete, and sign the Patient Enrollment Form for each patient.
 - Evaluate patients 3 months after the first infusion, 6 months after the first infusion, every 6 months thereafter to determine whether patients should continue on treatment, and for at least 6 months after discontinuing TYSABRI.
 - Submit to Biogen the "TYSABRI Patient Status Report and Reauthorization Questionnaire" 6 months after initiating treatment and every 6 months thereafter.
 - Complete an "Initial Discontinuation Questionnaire" when TYSABRI is discontinued and a "6-Month Discontinuation Questionnaire" following discontinuation of TYSABRI.
 - Report cases of PML, hospitalizations due to opportunistic infections, and deaths to Biogen at 1-800-456-2255 and to the Food and Drug Administration's MedWatch Program at 1-800-FDA-1088 as soon as possible.
- Patients must be enrolled in the TOUCH Prescribing Program, read the Medication Guide, understand the risks associated with TYSABRI, and complete and sign the Patient Enrollment Form.
- Pharmacies and infusion centers must be specially certified to dispense or infuse TYSABRI.

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Herpes Infections – Encephalitis, Meningitis and Acute Retinal Necrosis

- TYSABRI increases the risk of developing encephalitis and meningitis caused by herpes simplex and varicella zoster viruses.
- Serious, life-threatening, and sometimes fatal cases have been reported in the postmarketing setting in multiple sclerosis patients receiving TYSABRI.
- The duration of treatment with TYSABRI prior to onset ranged from a few months to several years.
- Monitor patients receiving TYSABRI for signs and symptoms of meningitis and encephalitis. If herpes encephalitis or meningitis occurs, TYSABRI should be discontinued, and appropriate treatment for herpes encephalitis/meningitis should be administered.
- Patients being administered TYSABRI are at a higher risk of acute retinal necrosis (ARN), a fulminant viral infection of the retina caused by the family of herpes viruses. Patients with eye symptoms such as decreased visual acuity, redness or eye pain should be referred for retinal screening as serious cases of ARN can lead to blindness of one or both eyes.
- Following clinical diagnosis of ARN consider discontinuation of TYSABRI.

Hepatotoxicity

- Clinically significant liver injury, including acute liver failure requiring transplant, has been reported in patients treated with TYSABRI in the postmarketing setting.
- Signs of liver injury, including markedly elevated serum hepatic enzymes and elevated total bilirubin, occurred as early as six days after the first dose; signs of liver injury have also been reported for the first time after multiple doses.
- In some patients, liver injury recurred upon rechallenge, providing evidence that TYSABRI caused the injury.
- 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.
- TYSABRI should be discontinued in patients with jaundice or other evidence of significant liver injury (e.g., laboratory evidence).

Hypersensitivity/Antibody Formation

- Hypersensitivity reactions have occurred in patients receiving TYSABRI, including serious systemic reactions (e.g., anaphylaxis) which occurred at an incidence of <1%.
- Reactions usually occur within 2 hours of the start of the infusion. Symptoms associated with these reactions can include urticaria, dizziness, fever, rash, rigors, pruritus, nausea, flushing, hypotension, dyspnea, and chest pain. Generally, these reactions are associated with antibodies to TYSABRI.
- If a hypersensitivity reaction occurs, discontinue administration of TYSABRI, and initiate appropriate therapy. Patients who experience a hypersensitivity reaction should not be re-treated with TYSABRI.
- Hypersensitivity reactions were more frequent in patients with antibodies to TYSABRI compared with patients who did not develop antibodies to TYSABRI in both MS and CD studies.
- Patients who receive TYSABRI for a short exposure (1 to 2 infusions) followed by an extended period without treatment are at higher risk of developing anti-natalizumab antibodies and/or hypersensitivity reactions on re-exposure, compared to patients who received regularly scheduled treatment.

Important Safety Information continued on next page.



Immunosuppression/Infections

- The immune system effects of TYSABRI may increase the risk for infections.
- In Study MS1, certain types of infections, including pneumonias and urinary tract infections (including serious cases), gastroenteritis, vaginal infections, tooth infections, tonsillitis, and herpes infections, occurred more often in TYSABRI-treated patients than in placebo-treated patients. One opportunistic infection, a cryptosporidial gastroenteritis with a prolonged course, was observed in a patient who received TYSABRI in Study MS1.
- In Studies MS1 and MS2, an increase in infections was seen in patients concurrently receiving short courses of corticosteroids. However, the increase in infections in TYSABRI-treated patients who received steroids was similar to the increase in placebo-treated patients who received steroids
- Concurrent use of antineoplastic, immunosuppressant, or immunomodulating agents may further increase the risk of infections over the risk observed with use of TYSABRI alone. The safety and efficacy of TYSABRI in combination with antineoplastic, immunosuppressant, or immunomodulating agents have not been established.
- In Studies MS1 and MS2, the rate of any type of infection was approximately 1.5 per patient-year in both TYSABRI-treated patients and placebo-treated patients
- In Study MS1, the incidence of serious infections was approximately 3% in TYSABRI-treated patients and in placebo-treated patients. Most patients did not interrupt treatment with TYSABRI during infections.
- In postmarketing experience, serious herpes infections have occurred.

Laboratory Test Abnormalities

- In clinical trials, TYSABRI was observed to induce increases in circulating lymphocytes, monocytes, eosinophils, basophils, and nucleated red blood cells. Observed changes persisted during TYSABRI exposure, but were reversible, returning to baseline levels usually within 16 weeks after the last dose. Elevations of neutrophils were not observed. TYSABRI induces mild decreases in hemoglobin levels (mean decrease of 0.6g/dL) that are frequently transient.

Thrombocytopenia

- Cases of thrombocytopenia, including immune thrombocytopenic purpura (ITP), have been reported with the use of TYSABRI in the postmarketing setting.
- Symptoms of thrombocytopenia may include easy bruising, abnormal bleeding, and petechiae.
- Delay in the diagnosis and treatment of thrombocytopenia may lead to serious and life-threatening sequelae. If thrombocytopenia is suspected, TYSABRI should be discontinued.
- Cases of neonatal thrombocytopenia, at times associated with anemia, have been reported in newborns with *in utero* exposure to TYSABRI. A CBC should be obtained in neonates with *in utero* exposure to TYSABRI.

Adverse Reactions

- The most common adverse reactions reported at an incidence of $\geq 10\%$ with TYSABRI and $\geq 2\%$ difference with placebo were headache (38% vs 33%), fatigue (27% vs 21%), infusion reactions (24% vs 18%), urinary tract infections (21% vs 17%), arthralgia (19% vs 14%), depression (19% vs 16%), pain in extremity (16% vs 14%), rash (12% vs 9%), gastroenteritis (11% vs 9%), and vaginitis* (10% vs 6%).

*Percentage based on female patients only.

- The most frequently reported serious adverse reactions in Study MS1 were infections (3.2% vs 2.6% placebo), including urinary tract infection (0.8% vs 0.3%) and pneumonia (0.6% vs 0%), acute hypersensitivity reactions (1.1% vs 0.3%, including anaphylaxis/anaphylactoid reaction [0.8% vs 0%]), depression (1.0% vs 1.0%, including suicidal ideation or attempt [0.6% vs 0.3%]), and cholelithiasis (1.0% vs 0.3%).
- Based on animal data, TYSABRI may cause fetal harm. TYSABRI should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.



References:

1. TYSABRI prescribing information. Cambridge, MA: Biogen.
2. Yousry TA, Major EO, Ryschewitsch 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. Cambridge, MA: Biogen.
4. Project Inform. Progressive multifocal leukoencephalopathy (PML). Available at: <http://www.projectinform.org/info/pml/index.shtml>. Accessed February 14, 2008.
5. What is Crohn's Disease? Crohn's & Colitis Foundation of America. <http://www.cdfa.org/what-are-crohns-and-colitis/what-is-crohns-disease/?referrer=https://www.google.com/>. Accessed June 24, 2016.

Please see the Prescribing Information, including **BOXED WARNING**, for more information

