Infusion Protocol

Natalizumab (Tysabri®)

Indication:

Natalizumab is indicated as monotherapy for the treatment of relapsing forms of multiple sclerosis, to include clinically isolated syndrome, relapsing-remitting disease and active secondary progressive disease, in adults. Natalizumab increases the risk of PML. When initiating and continuing treatment with Natalizumab, physicians should consider whether the expected benefit of natalizumab is sufficient to offset this risk.

Based on animal data, natalizumab may cause fetal harm. Natalizumab should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Infusion Protocols:

- TOUCH Training (Tysabri Outreach: Unified Commitment to Health) training required.
- 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.
- Under the TOUCH Prescribing Program (REMS program), only prescribers, pharmacies and infusion sites enrolled in the program can prescribe, distribute or infuse TYSABRI.
- TYSABRI must be administered only to patients who are enrolled in and meet all the conditions of the TOUCH Prescribing Program.
- To enroll in the TOUCH Prescribing Program, prescribers and patients are required to understand the risks of treatment with TYSABRI, including PML and other opportunistic infections.
- Enrollment in the TOUCH Prescribing Program is required to prescribe, distribute, administer or receive TYSABRI (www.tysabrihcp.com/en_us/home/touch-prescribing-program/touch-online.html) For TOUCH® Prescribing Program contact Biogen at 1-800-456-2255.

Dose: 300 mg every 28 days. (new data suggests extended dosing up to every 6 to 8 weeks. See attached publication.)

Supplied: 300 mg in 15 mL clear solution

Refrigerate vials between 36°F to 46°F (2°C and 8°C)

Reconstituted and Dilution:

Use aseptic technique to prepare solution for IV infusion.

Inspect the vial for particulate material and discoloration prior to dilution.

If visible particulates are observed and/or the liquid in the vial is discolored, do not use.

Withdraw 15 mL of natalizumab concentrate from the vial using a sterile needle and syringe. Inject the concentrate into 100 mL of 0.9% Sodium Chloride Injection, USP.

No other IV diluents may be used to prepare the natalizumab solution.

- Gently invert the natalizumab solution to mix completely. Do not shake.
- Inspect the solution visually for particulate material prior to administration.
- The final dosage solution has a concentration of 2.6 mg/mL.
- If natalizumab is not infused immediately, the solution can be refrigerated 36°F to 46°F (2°C and 8°C) up to 8 hours. Do not freeze diluted solution.

Pre-Infusion:

Labs: stratify JCV AB; varicella IGG, LFT, CBC, Chem 7

JCV AB Index >1.5 caution with continued dosing of natalizumab (2018 AAN guidelines recommend caution and consideration of PML risk with baseline index above 0.9).

Baseline MRI brain and cervical spine

Infusion:

Establish IV line.

No pre infusion medications necessary.

Labs: Chem 7, CBC, LFT monthly (stratify JCVab testing every 4 months with Index > 0.2; JCVab Index every 6 months with Index >0.2)

Complete Pre-Infusion Checklist with patient to determine if patient can be infused.

- If the patient cannot be infused, call neurologist for further evaluation.
- If the patient can be infused, proceed with next steps.

Call pharmacy to reconstitute 300 mg natalizumab in 100 mL normal saline.

Once mixed, natalizumab is infused immediately as it is stable at room temperature for 1 hour and stable if refrigerated up to 8 hours.

- Infuse natalizumab 300 mg in 100 mL 0.9% Sodium Chloride Injection, USP, over 1 hour (infusion rate 5 mg/minute).
    - If refrigerated, allow solution to warm to room temperature prior to infusion.
    - Do not administer TYSABRI as an IV push or bolus injection.
    - After the infusion is complete, flush with 0.9% Sodium Chloride Injection, USP.
    - Promptly discontinue the infusion upon the first observation of any signs or symptoms consistent with a hypersensitivity-type reaction.
- Observe patients during the infusion and for 1 hour after the infusion is complete.
- Use of filtration devices during administration has not been evaluated. Other medications should not be injected into infusion set side ports or mixed with natalizumab.

Safety:

Progressive Multifocal Leukoencephalopathy (PML): The presence of JCV AB, longer treatment (more than 2 years) with natalizumab and prior immunosuppressant use have all been shown to increase risk for development of PML with natalizumab. All patients should be continuously monitored for new signs or symptoms that could suggest PML.

Monitoring with MRI every 6 months in those positive for JCV AB and annually in those negative for JCV AB and as indicated for signs that may be consistent with PML.

Monitor every 4 months JCVab when Index > 0.2.

Herpes Infections: Encephalitis, Meningitis and Acute Retinal Necrosis

Hepatotoxicity: Significant liver injury may occur soon after the first dose or after multiple doses. Continuous monitoring of signs and symptoms suggestive of liver injury as well as liver function laboratory monitoring is recommended.

Hypersensitivity/Antibody Formation: serious anaphylaxis occurs in <1%

Infusion reaction: Occur within 2 hours of dosing to include: urticaria, dizziness, fever, rash, rigors, pruritus, nausea, flushing, hypotension, dyspnea and chest pain.

- Treat infusion reaction per infusion center protocol.
- Stop infusion for hypersensitivity reactions and suspect neutralizing antibody.
- Draw labs for NABs.
- Do not continue natalizumab infusion if NABs present or infusion reaction has occurred.

Immunosuppression/infection: Pneumonias and urinary tract infections (including serious cases), gastroenteritis, vaginal infections, tooth infections, tonsillitis and herpes infections occur. Serious infection occurred about 3%.

Adverse reaction: 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%)

Serious adverse reactions: Infections (3.2% vs 2.6%), 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%)

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 0.6 g/dL) that are frequently transient.

Discontinuation:

Monitoring for PML including signs and symptoms suggestive of PML and JCV AB lab monitoring should continue for 6 months after discontinuation of natalizumab.

Increased risk for relapse has been reported in the immediate time after natalizumab discontinuation. If switching DMTs, lessening time to initiation of the new DMT may help decrease this risk.

References:

Marianna LR, et al. Natalizumab Discontinuation and Treatment Strategies in Patients with Multiple Sclerosis (MS): A Retrospective Study from Two Italian MS Centers. Neurol Ther. 2015 Dec;4(2):147-57.

Natalizumab Criteria For Use: https://www.va.gov/formularyadvisor/DOC/111

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