**Mellen Center Approaches: Natalizumab (TYSABRI®)**

**Q: Who should be considered for natalizumab therapy?**

A: In the phase II and phase III trials of natalizumab only patients with relapsing forms of MS were enrolled. In the phase II trial 30% of the patients had secondary progressive MS patients with continued relapses. Regulatory agencies have limited the use of natalizumab to treating relapsing forms of multiple sclerosis.

In general, we consider natalizumab therapy for patients with continued disease activity despite the use of one or more disease modifying agents (i.e. Avonex®, Betaseron®, Copaxone®, Rebif®) or with aggressive disease characteristics where therapy with a higher risk/more effective agent is warranted, or when disease modifying agents are not sufficiently well tolerated to continue.


FDA labeling information.

**Q: Can steroids be used with natalizumab for a relapse and if so what format?**

A: Our approach is the same as in the pivotal trials. Steroid treatment was available for patients in the pivotal natalizumab trials having relapses. We use a standard course of steroids for relapses in patients on natalizumab. Such a treatment does not appear to confer increased risk in the subset of patients treated in this way. Long term steroids should not be used in such patients to reduce the risk of increasing immunosuppression. We do not adjust our natalizumab schedules for such steroid treatment but continue the 4 week protocol.

Reference: Polman 2006
**Q: What blood monitoring should be use for natalizumab patients?**

A: Recent post-marketing reports of elevated liver function tests has prompted closer monitoring of these tests in natalizumab treated patients. We monitor liver function tests (ALT, AST) at 0, 3, and 6 months and every 6 months thereafter while patients are on natalizumab therapy.

References: Consensus at Mellen Center, FDA labeling information

**Q: When should natalizumab antibodies be measured?**

A: In the pivotal studies approximately 6% of patients developed measurable natalizumab antibodies within months of beginning natalizumab. In patients with persistently positive antibodies, the therapeutic effects on relapses and MRI lesions was lost. Patients treated with natalizumab with < 3 infusions, and then re-treated after a hiatus appeared to have a higher rate of both infusion reactions and natalizumab antibodies.

Our approach is to check antibody levels at 6 months. If antibodies are positive and the patient is not doing well, we stop natalizumab. If the antibodies are positive but they are doing well we recheck at 9 months, following the patient closely for infusion reactions. We do not continue patients on natalizumab in the face of persistent anti-natalizumab antibodies.

Reference: Polman 2006

**Q: If patients have a minor infection (eg, urinary tract infection, upper respiratory tract infection), does the natalizumab dosing need to be changed?**

A: There is no need to change the dosing of natalizumab for minor infections. For unusual or unexpected infections, the treating physician should consider whether the infection is related in some way to the natalizumab effect and act accordingly.

Reference: Mellen Consensus

**Q: If patients are on another agent and switch to natalizumab, how much washout should there be?**

A: An international panel recommended the following washout periods:

For azathioprine, methotrexate, mycophenolate mofetil, mitoxantrone, and cyclophosphamide a washout period of at least 3 months or normalization of immune function. We agree with this recommendation.

For standard disease-modifying therapies (Avonex, Betaseron, Copaxone, Rebif), our consensus is that a reasonable time to wait would be 2 weeks.


**Q: What should prompt an evaluation for PML or other infection in natalizumab-treated patients?**

A: Features that should raise the issue of PML include new, focal, or subacutely progressive changes in clinical course. Of course, such changes can also occur with MS and need to be evaluated as well. Features that are more suggestive of PML clinically include visual field cuts, aphasia, and rapidly progressive cognitive deficits. Note that onset tends to be more subacute in PML than in MS but this may not distinguish the two conditions effectively. Also PML is uncommon in spinal cord and optic nerves while MS lesions are common in these areas.

There is at present no predictive blood, bone marrow or CSF test for the risk of PML. Good clinical surveillance is the best measure to assess for PML. Well trained infusion staff are the front line of such a surveillance program.

We avoid steroid use and continued natalizumab dosing during the evaluation for PML until it is clear that the source of symptoms is not related to PML.

References: Kappos 2007; Ransohoff 2007
**Q: How do we test for PML?**

A: We recommend that MRI scanning should be instituted as soon as possible when PML is suspected in natalizumab treated patients. Lesions may be found at the gray matter–white matter interface and tend to involve the subcortical white matter. This predilection accounts for the scalloped margins of the lesions. Lesions are initially multiple and discrete, but they eventually may coalesce into large lesions. Typically, lesions of PML are non-enhancing. The lesions may occur anywhere, but are most often seen in the parieto-occipital and frontal lobes. Despite these characteristics, there may be overlap in MRI appearance between PML and MS lesions.

We recommend that CSF should be tested for JC virus, the causative virus for PML. Its presence in the appropriate clinical picture is felt to be diagnostic for PML. Repeat CSF testing may be required if initial testing is negative.

Brain lesional biopsy may be required in cases where diagnosis is not apparent from the above testing.

Reference: Kappos 2007

**Q: What to consider in treatment of natalizumab associated PML?**

A: At present immune reconstitution appears to be the only viable treatment for PML occurring under any circumstance. In the MS population this means stopping natalizumab. Pharmacokinetic studies showed that natalizumab can be effectively removed from the blood compartment using plasmapheresis, and this treatment was used in post-marketing cases of PML. It is not clear how effective plasmapheresis is in the treatment of PML occurring with natalizumab therapy. Our consensus is to use plasmapheresis treatments every other day for a total of five treatments if PML emerges. Other medications are being considered such as Remeron® and Mefloquine® but are at present theoretical in efficacy.

Reference: Mellen Consensus; Khatri et al, Neurology, in press.

**Q: What routine MRI monitoring is reasonable in natalizumab-treated patients?**

A: At the Mellen Center, we do a baseline brain MRI prior to institution of natalizumab. We will often repeat the MRI if possible on the same MRI machine at 6 months and then annually or more often per clinical judgment. We will repeat MRI if there are new symptoms concerning for PML or other change in disease course.

Reference: Mellen Consensus

**Q: What treatment should be offered for natalizumab-treated patients with allergic reactions?**

Allergic reactions occurred in clinical trials in about 2% to 4% of natalizumab-treated patients. Most of these appear to be type 1 allergic reactions occurring during or within a short time after the infusion. These begin typically during or after the second infusion. If such reactions occur, natalizumab should be immediately stopped and not retried.

Treatment with the following is appropriate:

- Monitoring of blood pressure, respirations, and pulse closely until reaction resolves
- Benadryl® 50 mg IM/IV/PO
- Epinephrine injection appropriate for anaphylaxis (eg, 0.3-0.5 ml 1:1000 solution sc or IM q 15 minutes)
- Inhaled albuterol 0.5 mL 0.5% soln in 2.5 cc NS nebulized q15min
- IV fluids
- Oxygen, admission via emergency room, etc.

In general if reactions are significant or prolonged we have the patient transported to the emergency room for more acute care management.


Cases of type III reactions (serum sickness) have been documented with natalizumab. These are delayed reactions that may occur days after
treatment and may occur after a first dose. Symptoms are characterized by malaise, arthralgia, fever, pruritus and headache. Such symptoms may respond to a short course of oral steroids and removal of the natalizumab.

We do not try to re-dose patients with acute allergic reactions, since re-dosing can be associated with a more severe acute reaction. However, patients with type III reactions can be treated with a slower infusion, histamine blockers (H2 and H1), as well as steroids and Tylenol®.

Patient with both types of reactions may show natalizumab antibodies.


Q: What are the recommendations for pregnancy and family planning?

At present there are limited data about the use of natalizumab in pregnancy. This medication is a category C drug. This category states that: animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

We recommend a standard washout time from natalizumab (3 months) similar to other higher risk medication in MS. We recommend that patients use an acceptable form of birth control during natalizumab treatment if necessary. If they become pregnant during natalizumab treatment, we recommend that they stop natalizumab unless there are circumstances that require continuation.

If a woman becomes pregnant while taking TYSABRI, we recommend enrolling her in the TYSABRI Pregnancy Exposure Registry by calling 1-800-456-2255.

Reference Prescribing information for natalizumab.

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NOTE: The above is a consensus statement from the Mellen Center staff. This is not meant to be used as medical advice and does not constitute treatment recommendations for specific patient care. Information about medications is subject to change and package inserts and prescribing instructions should be reviewed prior to use. The above information may be subject to revision depending on changes in medical knowledge.