

Mellen Center Approaches: Natalizumab

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 active inflammation despite the use of one or more disease modifying agents or with aggressive disease characteristics where therapy with a higher risk/more effective agent is warranted, or when other disease modifying agents are not sufficiently well tolerated to continue.

Note that we will use natalizumab as an initial agent in patients with apparent aggressive/very active MS if the risk of MS worsening outweighs the risk of natalizumab.

REFERENCES

Miller DH et al. A controlled trial of natalizumab for relapsing multiple sclerosis. *NEJM* 2003;348:15-23

Rudick RA, et al. Natalizumab plus interferon beta-1a for relapsing multiple sclerosis. *NEJM* 2006;354:911-923

Ransohoff RM Natalizumab for Multiple Sclerosis *NEJM* 2007; 356(25): 2622–2629.

Kappos L, et al. Natalizumab treatment for multiple sclerosis: recommendations for patient selection and

monitoring. *Lancet Neurology* 2007;6:431-441

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. In general, long term steroids should be avoided 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.

However, clinical relapses after the first six months of natalizumab treatment are quite unusual and should serve as a red flag to trigger consideration of other etiologies, including progressive multifocal leukoencephalopathy, pseudo-relapse, secondary progression, anti-natalizumab antibodies, and intercurrent infection (i.e. urinary tract infection).

REFERENCES

Polman CH et al. A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. *NEJM* 2006; 354:899-910

Miller D et al. Differential diagnosis of suspected multiple sclerosis: a consensus approach. *Multiple Sclerosis* 2008;14:1157-1174

Q: Can modifications of natalizumab dosing be used, and if so, what?

A: Since the introduction of natalizumab, various dosing alternative have been proposed and tried in clinical practice. These include different dosing schedule (e.g. every 3 weeks, every 6 weeks, or other),
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Mellen Center Approaches: Natalizumab, continued

drug holidays, and dose adjustment for body mass. We have not found compelling evidence that these adjustments are more effective or safer than standard dosing, and are concerned that alternative strategies may be less effective or lead to rebound increase in disease activity (in the case of drug holidays). Observational studies of drug holidays suggest return of disease activity within a few months of natalizumab, particularly in patients with very active MS. We therefore use standard dosing in our patients unless there are compelling reasons for a different strategy.

REFERENCES

Kerbrat A et al. Natalizumab and drug holiday in clinical practice. *J Neurol Sci* 2011;308:98-102

Q: When should anti-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 benefits of natalizumab 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 for anti-natalizumab antibodies 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.

REFERENCES

Polman CH et al. A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. *NEJM* 2006; 354:899-910

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

A: If there is active inflammation, one can usually go right to natalizumab without any wash-out. If there is no active disease, then we generally recommend the following:

For injectable disease modifying therapies (Avonex, Betaseron, Copaxone, Rebif) our consensus is that there is no need to wait.

For newer agents such as fingolimod, teriflunomide, and dimethyl fumarate, there is no clear guidance. Wash-out periods with these therapies will depend upon the specific clinical situation (i.e. degree of disease activity, recovery from relapses, etc). Given the safety of natalizumab in JCV seronegative patients, prolonged wash-out before starting natalizumab is probably not necessary. For some therapies which reduce peripheral lymphocyte counts, it would be reasonable to wait for lymphocyte counts to normalize. This is typically about one month after fingolimod, but can be up to six months or more after dimethyl fumarate.

For azathioprine, methotrexate, mycophenolate mofetil, mitoxantrone, and cyclophosphamide a washout period of at least 3 months could be considered, although this would need to be weighed against the risk of return of disease activity.

For therapies with prolonged lymphopenia (i.e. rituximab and alemtuzumab), the appropriate wash-out before starting natalizumab is unknown. Again, the risk of return of disease activity needs to be weighed against the theoretical increased risk from immunosuppression.

REFERENCES

Kappos L et al. Natalizumab treatment for multiple sclerosis: recommendations for patient selection and monitoring. *Lancet Neurology* 2007;6:431-441

Q: If patients have a minor infection (e.g. 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.

REFERENCES

Mellen Consensus

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Mellen Center Approaches: Natalizumab, continued

Q: What are the main safety risks of natalizumab?

A: The main concern for clinicians and patients is the risk of patients developing progressive multifocal leukoencephalopathy (See below). However other significant risks occur with the use of natalizumab: hypersensitivity reactions including anaphylaxis, hepatotoxicity including liver failure requiring transplantation, and herpes encephalitis and meningitis (life-threatening and fatal cases have occurred). Patients having a hypersensitivity reaction should stop using natalizumab.

Other common adverse reactions to natalizumab (incidence >10%) include headache, fatigue, arthralgia, urinary tract infection, lower respiratory tract infection, gastroenteritis, vaginitis, depression, pain in extremity, abdominal discomfort, diarrhea, rash.

Q: What laboratory testing is routinely done while receiving treatment for natalizumab?

A. See table below:

	Pre-testing	2nd infusion	7th infusion	Every three months thereafter	Every six months thereafter
Liver Panel	X	X	X		X
Anti-JCV antibody test (STRATIFY JCV)	X		X	X	
Anti-natalizumab antibody test	X		X		

Q: Can PML be predicted in individual patients?

Three risk factors have been identified that are predictive of PML: previous exposure to JC virus (the causative agent of PML), previous treatment with chemotherapy, and duration of treatment. Low body mass may also be a risk factor. A JCV serology test (called STRATIFY JCV) is available through Quest Diagnostics, and the costs of this test is currently (2015) is covered by Biogen Idec for most non-

government-insured patients. About half of MS patients test positive for the JCV through the JCV STRATIFY test, and are at increased risk for PML. Chemotherapy and duration of treatment exposure (particularly beyond 2 years) also increase the risk of PML. The following table is an estimated risk of PML, using data from July 2012:

Estimated risk of natalizumab-related to PML according to currently known risk factors. These estimates of these risks will likely change over time, but the magnitude is likely to be similar.

	Prior Immunosuppressants?	Overall Risk	Risk Up to 24 Mo Therapy	Risk After 24 Mo Therapy
JC Virus Antibody Negative	No	~1:8,136	~1:45,184	~1:5,180
	Yes	~1:2,869	~1:15,935	~1:1,827
JC Virus Antibody Positive	No	~1:201	~1:1,130	~1:129
	Yes	~1:72	~1:398	~1:46

(Modified from Fox and Rudick (Neurol 2012;78:436-7) using PML data as of April 2014)

The recent introduction of a JCVab index has modified our approach. We will now consider initiating natalizumab in patients with an index less than 1.5 as risk of PML appears to remain low in this subgroup of patients. We will consider continuing natalizumab in patients on natalizumab if their index is less than 1.5.

REFERENCES

Fox RJ, Rudick RA. Risk stratification and patient counseling for natalizumab in multiple sclerosis. *Neurology* 2012;78:436-437

Q. How often should JCV serology be checked?

For STRATIFY JCV seronegative patients, current FDA recommendations include re-testing **every three months**, since some patients seroconvert, after which they have increased risk of PML. For patients who test positive after testing seronegative, repeat testing 1-3 months later could be considered to confirm the positive results, particularly if they were positive only on the “second step” assay. Approximately 2% of patients will seroconvert annually.

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Mellen Center Approach: Lemtrada (alemtuzumab), continued

Note that there are now cases of patients developing PML on natalizumab who are JCVAB negative. Thus, while the risk is lower, PML should still be considered in this population when new or worsening symptoms occur.

In JCV positive patients, we recommend continued JCVAB testing. Although not fully validated, a rise in JCV serology titre may be seen at the start of PML. Therefore, continued testing of JCV serology is recommended, even in patients who previously tested seropositive.

REFERENCES

Mellen Consensus; FDA labeling information

Q. Can natalizumab be used in patients who are seropositive for JCV?

A. For patients with very active disease which has not been sufficiently controlled with other disease modifying therapies, natalizumab may be considered in those who are seropositive for JCV with titers greater than 1.5. However our team has significant reservation about this medications' use under these circumstances, and recommends use of alternative medications if at all possible. Close clinical and radiologic follow-up is recommended to monitor for possible PML. Patient should continue to be counseled about the risk benefit ratio in this circumstance (i.e. risk of active MS vs risk of developing PML in view of seropositivity). More frequent imaging (i.e. every 3 months) is warranted in such patients.

REFERENCES

Mellen Consensus

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, new seizures, or 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.

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.

Very subtle cortical lesions may be an early indicator of PML and may not be appreciable without sequential careful MRI imaging.

REFERENCES

Kappos L, et al. Natalizumab treatment for multiple sclerosis: recommendations for patient selection and monitoring. *Lancet Neurology* 2007;6:431-441

Ransohoff RM Natalizumab for Multiple Sclerosis *NEJM* 2007; 356(25): 2622 - 2629.

Q: How do we evaluate a patient for possible PML?

A: We recommend that MRI scanning should be instituted as soon as possible when PML is suspected in natalizumab-treated patients. Natalizumab dosing should be halted until PML is ruled out. New lesions developing after six months of therapy (i.e. new lesions after an MRI obtained 6 months or more after starting natalizumab) in a patient negative for anti-natalizumab antibodies should be considered suspicious for PML. Lesions may be found at the gray matter–white matter interface, tend to involve the subcortical white matter, and tend to be irregularly shaped (i.e. not round or ovoid). This predilection accounts for the scalloped margins of the lesions. Lesions are initially multiple and discrete, but they eventually may coalesce into large lesions. Historically, lesions of PML are non-enhancing, but in natalizumab-related PML, 40% show enhancement, particularly at the lesion edge. 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.

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Mellen Center Approaches: Natalizumab, continued

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

REFERENCES

Kappos L, et al. Natalizumab treatment for multiple sclerosis: recommendations for patient selection and monitoring. *Lancet Neurology* 2007;6:431-441

Yousry TA, et al. MRI pattern in natalizumab-associated progressive multifocal leukoencephalopathy. *Ann Neurol* 2012;72:779-787

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.

REFERENCES

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. We perform MRI scans every 3-4 months where possible in patients who are JCvAB positive (index 1.5 or greater) for closer surveillance for PML based on data suggesting improved outcome with early identification of PML.

REFERENCES

Mellen Consensus

Q: How is natalizumab stopped, or how are patients transitioned to a different therapy?

For patients being transitioned off natalizumab or to another therapy (i.e. who are found to be JCv seropositive), there is no clear guidance on how to transition to another therapy. The RESTORE trial found disease activity returned 12-16 weeks after discontinuing therapy, and can sometimes be robust and difficult to control. Across groups of patients, the average disease activity does not appear to overshoot the pre-natalizumab disease activity. However, individual patients can have substantial over-shoot rebound.

A short or no wash-out could be considered in patients transitioning to a different therapy, particularly if they had significant disease activity prior to starting natalizumab.

Patients stopping natalizumab should receive careful follow-up, including a follow-up brain MRI about 16 weeks after the last dose of natalizumab.

REFERENCES

Mellen Consensus

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

Allergic reactions occurred in clinical trials in about 2-4% 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 (e.g. 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.

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Mellen Center Approaches: Natalizumab, continued

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

REFERENCES

Krause RS, Anaphylaxis, eMedicine, updated June 13th, 2006, <http://www.emedicine.com/emerg/TOPI25.htm>

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, pruritis 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.

REFERENCES

Krumbholz, M. et al. delayed Allergic reaction to natalizumab associated with early formation of neutralizing antibodies. *Arch Neurol* 2007;64:1331-1333

Hellwig K, et al. Allergic and non allergic delayed infusion reactions during natalizumab therapy. *Arch Neurol* 2008;65:656-658

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 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.

REFERENCES

Prescribing information for natalizumab.

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.