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Practical Clinical Guidelines for Natalizumab Treatment in Patients With Relapsing Multiple Sclerosis

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ABSTRACT

Natalizumab (TYSABRI®) was the first high-efficacy monoclonal antibody disease-modifying therapy (DMT) approved as a monotherapy for the treatment of adults with relapsing forms of multiple sclerosis (MS), including clinically isolated syndrome, relapsing-remitting MS, and active secondary progressive MS. Because natalizumab is administered by intravenous infusion, infusion nurses play a key role in the care of natalizumab-treated patients. In the 16 years since approval, substantial data have been gathered on the long-term, real-world effectiveness and safety of natalizumab. This article provides a synopsis of this data, as well as practical information for optimizing patient care. This includes information on strategies to mitigate the risk of progressive multifocal leukoencephalopathy in natalizumab-treated patients, natalizumab use during pregnancy, and use with vaccines. It also includes guidance on the preparation and administration of natalizumab and monitoring of natalizumab-treated patients.

Key words: disease-modifying therapy, guidelines, infusion, monoclonal antibodies, multiple sclerosis, natalizumab

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INTRODUCTION

Multiple sclerosis (MS) is an autoimmune-mediated neurodegenerative disease of the central nervous system (CNS). In young adults, it is the most common chronic neurologic disease, with a mean onset between 20 and 30 years of age.[1,2] The global prevalence of MS in 2020 was 35.9 per 100 000 people, with women at least twice as likely to be affected as men.[3] The pathological hallmarks of MS are inflammatory, demyelinating lesions, which can be visualized by magnetic resonance imaging (MRI), and axonal loss.[2] Symptoms of MS include, but are not limited to, unilateral changes in vision, impaired sensation in the torso or extremities or weakness in the extremities, paresthesia or sensory disturbances, dizziness, and fatigue.[2] Relapses are characterized by new or worsening symptoms present for at least 24 hours in the absence of fever or infection.[4] There are currently 9 classes of disease-modifying therapies (DMTs) approved for the treatment of relapsing forms of MS, with varying routes of administration, including intravenous infusions.[2] One such infusible high-efficacy DMT approved for use in adults with relapsing MS (RMS) is natalizumab (TYSABRI®, Biogen).

Infusion nurses play a key role in the administration and monitoring of natalizumab-treated patients. Thus, an understanding of the mechanism of action, as well as the efficacy/effectiveness and safety profile, will be useful in clinical practice. This narrative review provides an overview of data supporting the effective and safe use of natalizumab in patients with RMS. Utilizing combined clinical experience and medication knowledge, the authors outline and discuss key practical clinical guidance for infusion nurses caring for natalizumab-treated patients, including preparation, administration, and monitoring of the natalizumab infusion.

As described in the United States Prescribing Information, the recommended dose of natalizumab is 300 mg intravenous infusion over 1 hour every 4 weeks (Q4W).[5] Natalizumab is believed to work by binding to α4-integrins, which are expressed on the surface of all leukocytes, except for neutrophils, blocking their ability to interact with vascular cell adhesion molecule-1 (VCAM-1; Figure 1). Blocking the interaction between α4-integrin and VCAM-1 prevents the transmigration of leukocytes across the blood–brain barrier. Natalizumab treatment, thereby, retains leukocytes in the periphery, without depleting them. This results in an elevation, within normal ranges, in peripheral leukocytes, including lymphocytes but not neutrophils.[6] These changes persist while on treatment but are reversible, returning to pretreatment levels usually within 16 weeks after the last natalizumab dose.[5,6]

Efficacy and Long-Term Effectiveness of Natalizumab

Natalizumab was shown to significantly reduce clinical and MRI disease activity over its 2-year, placebo-controlled, double-blinded randomized Natalizumab Safety and Efficacy in Relapsing-Remitting MS (AFFIRM) phase 3 clinical trial (Table 1).[5,7] A post hoc analysis of AFFIRM demonstrated that natalizumab has a rapid onset of clinical efficacy, with the difference in the cumulative probability of relapse first observed at day 42 between natalizumab- and placebo-treated patients.[8] Natalizumab also has a rapid onset of MRI efficacy, as evident from the results of its phase 2, randomized, placebo-controlled, double-blind study, which showed that the effect of natalizumab on reducing gadolinium-enhancing (Gd+) lesions was evident after 1 month of treatment.[9]

Long-term effectiveness of natalizumab has been investigated in the phase 4 TYSABRI Observational Program (TOP), the longest ongoing, open-label, multinational, observational study, which follows over 6000 patients with relapsing-remitting MS (RRMS). The 10-year interim results of TOP demonstrated sustained decreases in annualized relapse rate with natalizumab treatment (Table 2).[10] The STRIVE (Study of TYSABRI in Early Relapsing Remitting Multiple Sclerosis in Anti-JCV Antibody Negative Patients) study is the only other prospective observational phase 4 study examining the long-term effectiveness of natalizumab in early RRMS patients. The results from STRIVE further highlighted the long-term effectiveness of natalizumab with respect to clinical, MRI, and patient-reported outcomes (PROs), including quality of life (Table 3).[11,12]

CONFLICTS OF INTEREST AND SOURCE OF FUNDING

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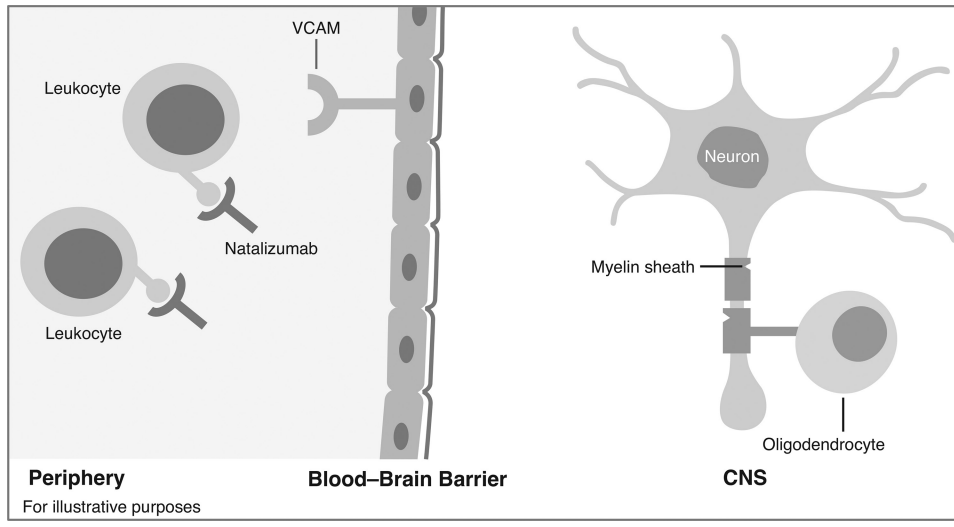


Figure 1 Proposed mechanism of action of natalizumab (TYSABRI). *Abbreviations: CNS, central nervous system; VCAM, vascular cell adhesion molecule.*

Long-Term Safety of Natalizumab

Natalizumab has a well-characterized safety profile, with 16 years of postmarketing data to date. In the AFFIRM pivotal study, the most common adverse events (incidence ≥25%) were headache and fatigue (Table 4).[5,7] In the TOP 10-year interim analysis, which assessed the incidence and pattern of serious adverse events (SAEs), 13.5% of patients experienced ≥1 SAE, with 4.7% of patients experiencing ≥1 SAE related or possibly related to natalizumab.[10] The most frequently reported SAEs, at an incidence of 4.1%, were in the system organ class infections and infestations, with the most commonly reported infections being progressive multifocal leukoencephalopathy (PML; 0.9%), pneumonia (0.4%), urinary tract infection (UTI; 0.3%), and herpes zoster (0.3%; Table 5). Immune reconstitution inflammatory syndrome (IRIS), which is known to occur in natalizumab-treated patients who develop PML and subsequently discontinue natalizumab, was reported in 0.9% of patients.[5] Malignancies were reported in 1.1% of patients, with breast cancer being the most common. However, the breast cancer incidence rate (86.7 per 100 000 patient-years) was consistent with rates reported by the Surveillance, Epidemiology, and End Results (SEER) program[13] and GLOBOCAN.[14] Hepatic SAEs were reported in 0.2% of patients.[10]

TABLE 1

AFFIRM 2-Year Clinical and MRI Results

	Natalizumab (n = 627)	Placebo (n = 315)
Clinical end points		
Cumulative probability of confirmed disability worsening[a,b]	17%	29%
Relative risk reduction vs placebo	42%	
Annualized relapse rate	0.22	0.67
Relative risk reduction vs placebo	67%	
MRI end points		
Patients with no new or newly enlarging T2 lesions	57%	15%
Patients with no Gd-enhancing lesions	97%	72%

Abbreviations: Gd, gadolinium; MRI, magnetic resonance imaging.
[a]Primary end point.
[b]Confirmed disability worsening was defined as an increase, confirmed 12 weeks later, of ≥1.0 point from a baseline Expanded Disability Status Scale (EDSS) score of ≥1.0, or ≥1.5 points from a baseline EDSS score of 0.0.

TABLE 2

TOP 10-Year Interim Clinical Results

Clinical End Point[a]	10 Years
Annualized relapse rate	0.15 (95% CI, 0.14–0.15)
Relative risk reduction	92.5%[b]
Cumulative probability of confirmed disability worsening[c]	27.8%
Cumulative probability of confirmed disability improvement[d]	33.1%

Abbreviation: TOP, TYSABRI Observational Program.
[a]The clinical end points were secondary end points in TOP; the primary end point was the incidence and pattern of serious adverse events.
[b]Relative to the ARR of 1.99 (95% CI, 1.97–2.02) in the year prior to starting natalizumab.
[c]Confirmed disability worsening was defined as an increase, confirmed 24 weeks later, of ≥0.5 point from a baseline Expanded Disability Status Scale (EDSS) score of ≥6.0, ≥1.0 point from a baseline EDSS score of ≥1.0 to <6.0 or ≥1.5 points from a baseline EDSS score of 0.0.
[d]Confirmed disability improvement was defined as a decrease of ≥1.0 point from baseline score, confirmed 24 weeks later, among patients with baseline EDSS scores ≥2.0.

TABLE 3

STRIVE Clinical, MRI, and PRO Results

End Point	Year 1	Year 2	Year 3	Year 4
Patients with NEDA,[a] %	56.1[b]	73.6[b]	71.4	74.8
Patients with clinical NEDA, %	81.0	85.1	84.6[b]	91.9[b]
Patients with MRI NEDA, %	69.9	88.0	85.9	83.7
Patients with clinically meaningful improvement in SDMT,[c] %	41.9	49.4	54.1	54.0
Patients experiencing stability or improvement in MSIS-29,[d] %				
Physical	—	—	—	88.5
Psychological	—	—	—	91.3

Abbreviations: CDW, confirmed disability worsening; MRI, magnetic resonance imaging; MS, multiple sclerosis; MSIS, Multiple Sclerosis Impact Scale; NEDA, no evidence of disease activity; PRO, patient-reported outcome; SDMT, Symbol Digit Modalities Test.
Dashes indicate not reported.
[a]NEDA included attainment of both clinical NEDA, defined as no relapses and no 24-week CDW, and MRI NEDA, defined as no gadolinium-enhancing lesions and no new or newly enlarging T2 lesions.
[b]Primary end points.
[c]A clinically meaningful improvement in SDMT was defined as an increase of ≥4 points in the patient's SDMT score compared with baseline. This signifies an improvement in the patient's cognitive processing speed.
[d]MSIS-29, which is a patient-reported outcome that assesses the physical and psychological impact of MS, was included to measure quality of life.

Progressive Multifocal Leukoencephalopathy

PML, one of the SAEs associated with natalizumab, is a rare, progressive, and potentially fatal opportunistic infection of the brain caused by mutated pathogenic forms of the John Cunningham virus (JCV) that typically only occurs in immunocompromised patients. It is believed that the mutated forms of the virus infect glial cells of the CNS, ultimately leading to destructive demyelination.[15] Mutated forms of JCV can also infect cerebellar granule cell neurons leading to JCV granule cell neuronopathy (GCN), which can occur with or without concomitant PML and should be managed similarly to PML.[5] In the US prescribing information, natalizumab has a black box warning on PML. As a result, natalizumab is only available in the United States through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the TOUCH® Prescribing Program. This REMS program requires certification of prescribers, pharmacies, and infusion centers, as well as enrollment of every patient receiving natalizumab. In accordance with the REMS program, prior to each infusion, clinicians should assess patients for potential new signs or symptoms of PML.

Symptoms associated with PML are diverse, progress over days to weeks, and can include, but are not limited to, progressive weakness on one side of the body or clumsiness of limbs, disturbance of vision, and changes in thinking, memory, and orientation, leading to confusion and personality changes.[5] It is important to distinguish symptoms suggestive of PML from those of a pseudo-relapse or relapse. A pseudo-relapse, which has an acute onset, is typically associated with an increase in body temperature due to an infection, exercise, or heat exposure and generally resolves when the causative physiological stress has been removed or resolved.[4] In contrast, an MS relapse is defined as an acute onset of new or worsening symptoms present for at least 24 hours in the absence of fever or infection (Figure 2).[4]

TABLE 4

Incidence of Adverse Events Occurring in ≥10% of Patients Treated With Natalizumab With a ≥2% Difference From Placebo in AFFIRM

Adverse Event	Natalizumab (n = 627)	Placebo (n = 312)
Headache	38%	33%
Fatigue	27%	21%
Infusion reactions[a]	24%	18%
Urinary tract infection	21%	17%
Arthralgia	19%	14%
Depression	19%	16%
Pain in extremity	16%	14%
Rash	12%	9%
Gastroenteritis	11%	9%
Vaginitis[b]	10%	6%

[a]Infusion reactions were defined as any event that occurred within 2 hours after the start of the infusion.
[b]Percentage based on female patients only.

PML Monitoring and Diagnosis

Infusion nurses, who see patients on a regular basis and perform the preinfusion checklist, play a critical role in

TABLE 5

Incidence of Serious Adverse Events Occurring in ≥10 Patients in TOP[a]

SAE, n (%)[b]	n = 6148; n (%)
IRIS[c]	54 (0.9)
PML, confirmed	53 (0.9)
Abortion spontaneous	37 (0.6)
Hypersensitivity	26 (0.4)
Pneumonia	23 (0.4)
Urinary tract infection	20 (0.3)
Fall	19 (0.3)
Depression	18 (0.3)
Epilepsy	18 (0.3)
Herpes zoster	17 (0.3)
Breast cancer	12 (0.2)
Intervertebral disc protrusion	12 (0.2)
Escherichia urinary tract infection	12 (0.2)
Suicide attempt	11 (0.2)
Pulmonary embolism	10 (0.2)
Pyelonephritis	10 (0.2)

Abbreviations: IRIS, immune reconstitution inflammatory syndrome; PML, progressive multifocal leukoencephalopathy; SAE, serious adverse event; TOP, TYSABRI Observational Program.

[a]Patients were enrolled from Germany, the Czech Republic, Belgium, Italy, Canada, the Netherlands, Norway, Finland, France, Slovakia, Australia, Great Britain, Greece, Spain, Mexico, Portugal, and Argentina.

[b]Each patient was counted only once within each preferred term. Multiple sclerosis was also reported as an SAE in 15 patients.

[c]One case of IRIS was not associated with PML.

monitoring for potential clinical signs or symptoms suggestive of PML. Infusion nurses familiar with a patient may detect subtle changes relative to previous infusions. They may also have a rapport with a caregiver or family member who can provide relevant clinical information. If there are clinical signs or symptoms suggestive of PML, natalizumab should be withheld, and the prescriber should be contacted immediately. It is imperative that the patient be evaluated by the prescriber, and an MRI and lumbar puncture should be performed as soon as possible (Figure 3).

Following the lumbar puncture, the cerebrospinal fluid (CSF) samples, which should be free of blood contamination, must be tested for JCV DNA using an ultrasensitive quantitative polymerase chain reaction (qPCR) assay (lower limit of detection <10 copies per milliliter). The utilization of an ultrasensitive qPCR is critically important, as there have been confirmed PML cases where the JCV DNA viral count is very low.[16] Furthermore, the detection of JCV DNA in the CSF, along with compatible imaging findings and/or clinical features, is sufficient to diagnose a patient with PML.[17] It is imperative to report suspected PML cases to the manufacturer as soon as possible. Importantly, if initial investigations prove negative but clinical suspicion for PML still remains, natalizumab should not be restarted, and further testing should be conducted.[5]

Asymptomatic PML: Importance of MRI Surveillance

It is important to note that PML can be diagnosed in the absence of clinical signs or symptoms. Research has found that when PML is diagnosed without clinical symptoms, based on MRI findings and the detection of JCV DNA in the CSF, it is associated with lower PML-related mortality and morbidity compared to PML with clinical symptoms at diagnosis.[18] Therefore, monitoring for radiological signs suggestive of PML is essential. For PML surveillance, the recent consensus paper of the Magnetic Resonance Imaging in MS (MAGNIMS) study group, the Consortium of Multiple Sclerosis Centers (CMSC), and the North American Imaging in Multiple Sclerosis (NAIMS) Cooperative recommends an abbreviated MRI protocol, including fluid-attenuated inversion recovery (FLAIR), as well as T2-weighted and diffusion-weighted imaging sequences, with more frequent monitoring for patients at high risk for PML.[19]

PML Risk Mitigation

More than 15 years of research by Biogen has led to a better understanding of natalizumab-associated PML risk. Unlike other MS DMTs associated with PML, 3 risk factors are known to increase the risk of natalizumab-associated PML.[19] Attention to these factors enables clinicians to better mitigate PML risk in natalizumab-treated patients.

Stratify JCV™ Antibody Assay

The first risk factor is the presence of anti-JCV antibodies. As JCV infections are asymptomatic, a health care provider can only determine if someone has been infected with JCV by collecting a serum/plasma sample and sending it to a laboratory to run an anti-JCV antibody assay. As the prevalence of anti-JCV antibodies in the adult population is reported to be between 50% and 60%,[20] it is important to test patients considering or receiving natalizumab for anti-JCV antibodies.

The Stratify JCV™ antibody assay, codeveloped and subsidized by Biogen, has been the only assay used in research regarding natalizumab-associated PML (Figure 4).[20] This assay is a 2-step enzyme-linked immunosorbent assay (ELISA). The first step of the assay is known as the screening/detection test; this step yields an index value. If the index value of a sample is <0.2, the patient's test result is negative, meaning that anti-JCV antibodies were not detected. In comparison, if the index value of a sample is >0.4, the patient's test result is positive, meaning that anti-JCV antibodies were detected. In circumstances where the index

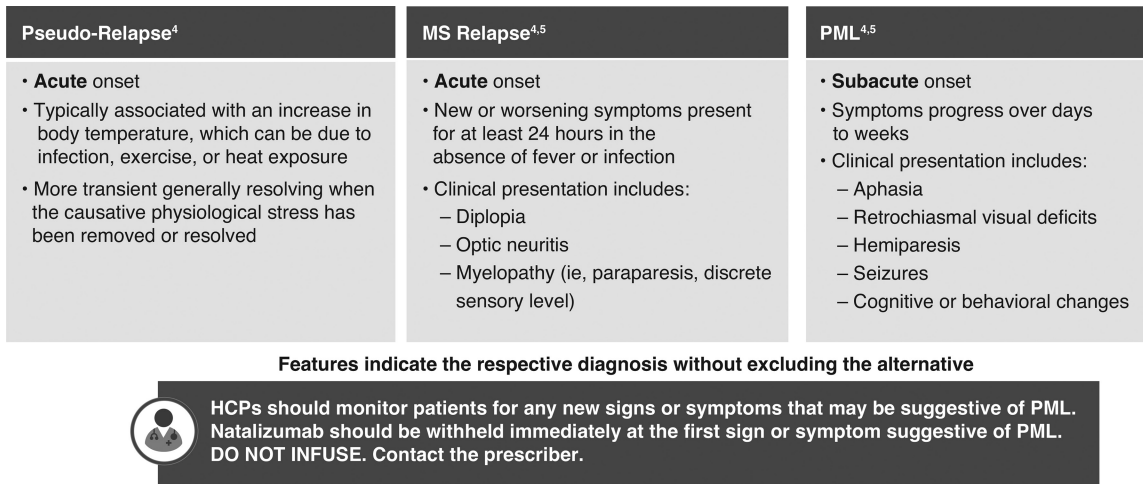


Figure 2 Differentiating clinical features: pseudo-relapse versus MS relapse versus symptomatic PML. *Abbreviations: HCP, health care professional; MS, multiple sclerosis; PML, progressive multifocal leukoencephalopathy.*

value of a sample is between 0.2 and 0.4, which may be referred to on the test result documentation as "indeterminate," the second step of the Stratify JCV antibody assay, known as the inhibition test, is needed to determine whether the patient's sample is negative or positive for anti-JCV antibodies.[20] Therefore, there are only 2 potential results for the Stratify JCV antibody assay: negative or positive.

Anti-JCV Antibody-Negative Patients

Once a patient's anti-JCV antibody status is known, it can then be utilized to determine the patient's estimated PML risk. If a patient is negative for anti-JCV antibodies, that patient's PML risk estimate is 0.07 per 1000 patients (Figure 5).[21] It is important to note that patients who are negative are still at risk of being infected with JCV and, thus, should be retested periodically, according to the US prescribing information.[5] The frequency of retesting is dependent on clinical discretion and varies widely in practice; clinicians may retest for anti-JCV antibodies monthly, every 3 months, or every 6 months.

There are 2 reasons patients who are negative for anti-JCV antibodies may still be at risk for the development of PML and should undergo periodic retesting. First, as with all assays, there is an inherent risk of a false-negative result, which means that the assay does not detect what is being tested even though it is present. The estimated false-negative rate for the Stratify JCV antibody assay is low (2.2%–3.0%).[5,20] Some circumstances may lead to the loss of antibodies, thereby indirectly causing a false-negative test result. One such situation is collecting a sample too soon after a patient has undergone plasma exchange (PLEX), which removes serum antibodies, including anti-JCV antibodies. For this reason, it is advised

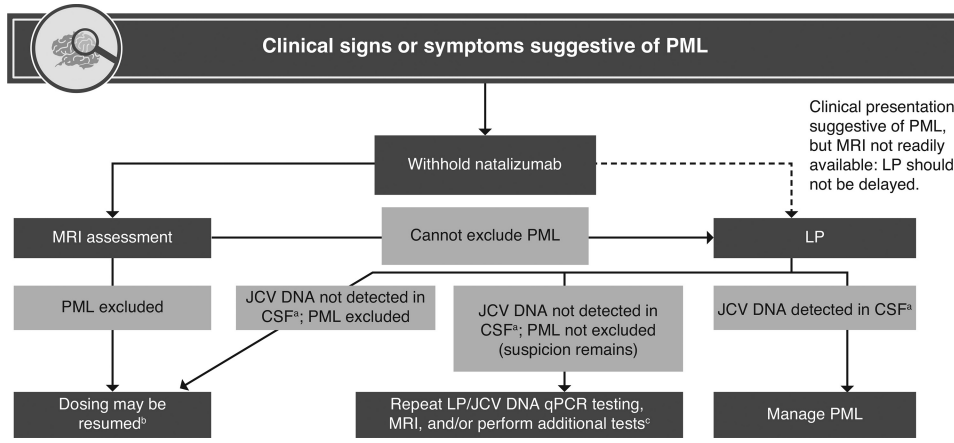


Figure 3 Steps to follow if you have a suspected PML case based on clinical signs/symptoms. *Abbreviations: CSF, cerebrospinal fluid; JCV, John Cunningham virus; LP, lumbar puncture; MRI, magnetic resonance imaging; MS, multiple sclerosis; PCR, polymerase chain reaction; PML, progressive multifocal leukoencephalopathy; qPCR, quantitative polymerase chain reaction.* [a]Ensure utilization of an ultrasensitive quantitative PCR assay (lower limit of detection <10 copies/ mL). [b]TYSABRI should be restarted only if the diagnosis of PML is excluded and if deemed appropriate for the ongoing treatment of MS. [c]For non-MS or PML differential diagnoses. If unable to detect JCV DNA in CSF after repeat LPs but PML suspicion remains, consider a brain biopsy.

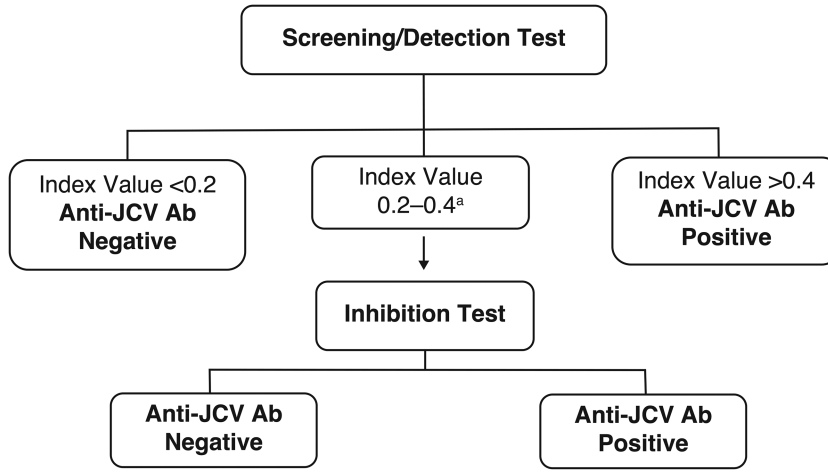
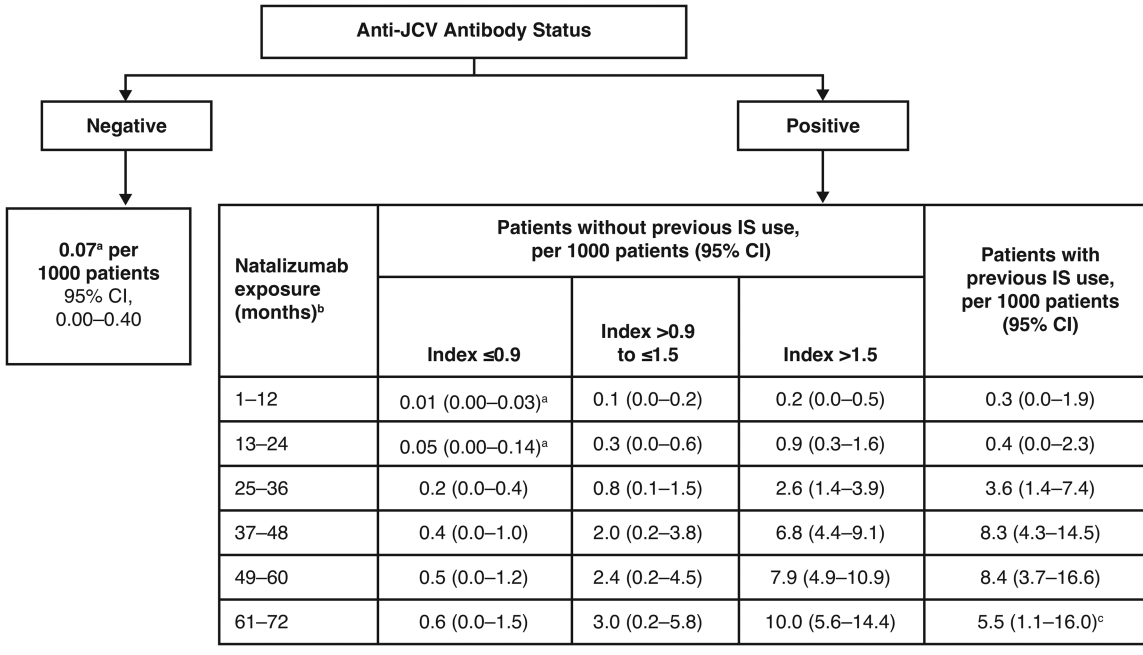


Figure 4 Stratify JCV™ antibody assay. *Abbreviations: Ab, antibody; JCV, John Cunningham (JC) virus.* [a]Samples with an index value between 0.2 and 0.4 may be referred to on the test result documentation as "indeterminate." In these circumstances, the second step of Stratify JCV antibody assay, known as the inhibition test, is run to determine whether the patient's sample is anti-JCV antibody negative or positive. Reprinted from *J Clin Virol*., vol. 57, Lee P, Plavina T, Castro A, et al, A second-generation ELISA (STRATIFY JCV DxSelect) for detection of JC virus antibodies in human serum and plasma to support progressive multifocal leukoencephalopathy risk stratification, pages 141-146, copyright 2013, with permission from Elsevier.

to wait at least 2 weeks after PLEX before testing for anti-JCV antibodies.[5]

The second reason a patient who has tested negative for anti-JCV antibodies may still be at risk of developing PML is that the patient could, at some point, become infected with JCV, resulting in the person testing positive on the anti-JCV antibody assay. Two distinct terms are used to describe this in the literature. The first is referred to as, "serostatus change," which means that the patient's most recent test result is anti-JCV antibody positive in contrast to that individual's previous test result, which was anti-JCV antibody negative. This is distinct from the second term, "seroconversion," which requires that the patient's test result not only change from anti-JCV antibody negative to



Natalizumab exposure (months)[b]	Patients without previous IS use, per 1000 patients (95% CI)			Patients with previous IS use, per 1000 patients (95% CI)
	Index ≤0.9	Index >0.9 to ≤1.5	Index >1.5	
1–12	0.01 (0.00–0.03)[a]	0.1 (0.0–0.2)	0.2 (0.0–0.5)	0.3 (0.0–1.9)
13–24	0.05 (0.00–0.14)[a]	0.3 (0.0–0.6)	0.9 (0.3–1.6)	0.4 (0.0–2.3)
25–36	0.2 (0.0–0.4)	0.8 (0.1–1.5)	2.6 (1.4–3.9)	3.6 (1.4–7.4)
37–48	0.4 (0.0–1.0)	2.0 (0.2–3.8)	6.8 (4.4–9.1)	8.3 (4.3–14.5)
49–60	0.5 (0.0–1.2)	2.4 (0.2–4.5)	7.9 (4.9–10.9)	8.4 (3.7–16.6)
61–72	0.6 (0.0–1.5)	3.0 (0.2–5.8)	10.0 (5.6–14.4)	5.5 (1.1–16.0)[c]

Figure 5 Current PML risk estimates. *Abbreviations: CI, confidence interval; IS, immunosuppressant; JCV, John Cunningham virus; PML, progressive multifocal leukoencephalopathy*. Conditional probability of developing PML using the life table method in each year of treatment with multiple imputation used to account for missing data in the pooled cohort (n = 21 696). [a]Although estimates below 0.1 per 1000 patients were rounded up to 0.1 per 1000 patients for regulatory documents and management guidelines, these estimates are shown with greater precision in this manuscript. [b]Data beyond 6 years of treatment are scarce. [c]Variability might be due to small sample size. Reprinted from *Lancet Neurol*, vol. 16, Ho PR, Koendgen H, Campbell N, et al., Risk of natalizumab-associated progressive multifocal leukoencephalopathy in patients with multiple sclerosis: a retrospective analysis of data from four clinical studies, pages 925-933, copyright 2017, with permission from Elsevier.

positive but also remain positive in subsequent testing.[5] A seroconversion rate of 3% to 8% annually in patients with MS is reported in the US prescribing information for natalizumab.[5]

When reading literature describing anti-JCV antibody serostatus over time, it is imperative to examine whether the authors are looking at serostatus change or seroconversion, as the results will differ. This is because some patients' anti-JCV antibody status may subsequently change back to negative status; these patients would meet the criteria for serostatus change but not seroconversion. This may occur in cases where the assay yields a false-positive test result. False-positive results can occur if a sample is collected too soon after a patient has undergone an intravenous immunoglobulin (IVIg) infusion. As IVIg preparations are pooled from healthy donors, approximately 50% to 60% of whom are expected to be positive for anti-JCV antibodies, an IVIg infusion may cause the passive transfer of anti-JCV antibodies, causing a positive test result in the absence of patient exposure to JCV. To avoid false-positive test results, it is recommended to wait at least 6 months (5 half-lives) after an IVIg infusion before testing for anti-JCV antibodies.[5]

Anti-JCV Antibody-Positive Patients

A positive anti-JCV antibody test does not mean that the patient has PML or will ultimately develop PML; it means that the patient has an increased risk of developing PML compared with a patient who is negative for anti-JCV antibodies. PML risk in patients who test positive for anti-JCV antibodies can be further stratified by the other 2 known risk factors: duration of natalizumab exposure and previous immunosuppressant use (Figure 5). The current algorithm provides PML risk estimates for up to 72 months of natalizumab exposure for anti-JCV antibody-positive patients, dependent on their previous immunosuppressant use.

Biogen considers previous treatment with the following medications as, "previous immunosuppressant use": mitoxantrone, azathioprine, methotrexate, cyclophosphamide, mycophenolate mofetil, or other, which includes immunosuppressive agents such as ciclosporin, tacrolimus, docetaxel, fluorouracil, and temsirolimus.[21] If a patient who is positive for anti-JCV antibodies has not previously used/taken the above immunosuppressants, that person's estimated PML risk can be further stratified by their index value (Figure 5). This algorithm, which is based on patient-level data, supports individualized benefit–risk discussions and patient management by providing a forward-looking estimate of yearly PML risk in patients remaining on natalizumab. It differs from the algorithm included in the US prescribing information, which only includes US patients and does not further stratify risk by anti-JCV antibody index. It is important to note that the US prescribing information does not mention any restrictions as to the length of time a patient can be on natalizumab. Therefore, a patient can remain on natalizumab as long as both the prescriber and patient are comfortable with the benefit-risk profile.

As mentioned above, the clinical utility of the index value is only in anti-JCV antibody-positive patients who have not had previous immunosuppressant use. The estimated PML risk in an anti-JCV antibody-positive patient without prior immunosuppressant use varies depending on the index category (ie, $\leq$0.9, $>$0.9 to $\leq$1.5, $>$1.5) that the patient falls under (Figure 5).[21] Therefore, in anti-JCV antibody-positive patients without previous immunosuppressant use, the stability of the index value over time is of concern to clinicians when determining PML risk. Data show that, at a population level, the index value is stable over time[22,23]; however, the index value may change over time in an individual patient. Possible reasons for an increase in the anti-JCV antibody index value in a specific patient include reinfection or reactivation of the JCV.[24]

Extended-Interval Dosing

An additional, more recent strategy used to mitigate natalizumab-associated PML risk in anti-JCV antibody-positive patients is extended-interval dosing (EID). This PML risk mitigation strategy was initially proposed and tested by a group of MS clinicians[25] and subsequently confirmed through analyses of patient data from the TOUCH® Prescribing Program, the largest data source on natalizumab-associated PML.[26-30] These TOUCH analyses, which included only those patients who were positive for anti-JCV antibodies, have been conducted annually since 2017 and have consistently shown that natalizumab EID, with an average dosing interval of approximately every 6 weeks (Q6W), is associated with a significantly lower risk of PML in comparison with standard-interval dosing of Q4W (ie, $\geq$80% relative reduction).[26-30] It is important to remember that EID reduces the risk of PML but does not eliminate the risk. The natalizumab pivotal trial AFFIRM included only Q4W dosing and, therefore, did not examine the efficacy of the EID. However, research has shown a temporal relationship between the reduction in the median saturation/occupancy of α4-integrin by natalizumab and the appearance of Gd+ lesions between 8 and 12 weeks after the last dose.[31] A recent phase 3b study examined the ability of Q6W dosing to maintain effectiveness in patients who were stable on natalizumab Q4W dosing, meaning no relapses in the 12 months prior to randomization and no Gd+ lesions on the screening MRI. The results of this study (NOVA) provide supportive evidence that natalizumab Q6W dosing can maintain MRI and clinical effectiveness in patients who were stable on natalizumab Q4W dosing for at least 1 year.[32]

Role of Infusion Nurses in the Treatment of RMS With Natalizumab

Infusion nurses trained and certified in the administration of natalizumab will begin interacting with RMS patients when natalizumab is initiated and may maintain a relationship throughout treatment. As MS is a chronic neurodegenerative disease, patients need to be educated on the

importance of remaining adherent to their infusion schedule in accordance with their prescribing clinician's orders. Infusion nurses are ideally suited to promote and support adherence. In addition to administering therapy, infusion nurses proactively assess the patient's tolerance of therapy, monitor for AEs/SAEs, and answer questions.

Preinfusion Checklist

As part of the US REMS program, infusion nurses are required to complete and submit a preinfusion checklist, which includes 3 steps, prior to every natalizumab infusion. First, the infusion nurse needs to confirm that the patient is authorized through the TOUCH Prescribing Program to receive the drug. If the authorization cannot be verified, the patient cannot be infused and should be referred to their prescriber. Second, the infusion nurse needs to ensure that the patient has received, read, and understood the patient medication guide for natalizumab. If not, the nurse must provide the medication guide to the patient. Finally, the infusion nurse needs to ask 3 questions, captured on the preinfusion checklist, pertaining to whether the patient has had, in the past month, any new or worsening medical problems that have persisted over several days, as well as any medical conditions or medications that can weaken their immune system. If the patient answers, "yes" to any of the 3 questions asked, the nurse should contact the prescriber or their representative and review the patient's answers with them. The patient can only be infused if the prescriber authorizes the infusion after discussing the patient's answers.

Once it is confirmed that the patient can receive their natalizumab infusion, the infusion nurse can prepare the medication and administer it. Guidelines for the preparation, administration, and monitoring of natalizumab-treated patients are shown in Appendix 1.

Preparation

In the preparation of the infusion, special attention should be given to preserving the integrity of the natalizumab molecule. Health care providers preparing natalizumab can minimize structural risk to the protein by avoiding agitation of the 15-mL vial of the solution containing natalizumab 300 mg (20 mg/mL). If a vial of natalizumab is exposed to temperatures up to 25°C (77°F) or down to 0°C (32°F) for <24 hours, there is no expected impact on the shelf life of the product. Such vials can be used through the stamped expiration date, provided that the proper storage conditions are subsequently followed.

After following proper handwashing and aseptic techniques, the medication should be aspirated slowly into a 20-mL syringe with a 20- to 18-gauge sterile needle, avoiding bubbles, and carefully injecting the medication into the diluent (100-mL prefilled 0.9% saline bag for intravenous [IV] infusion). The diluted drug in the IV bag should be gently inverted to mix completely,[33] and shaking should be avoided.

When preparing medication from the natalizumab vial, it is important to minimize the risk of particulate matter from the rubber stopper entering the infusion solution. Particulate matter can elicit a systemic reaction to latex or embolization in the patient receiving the infusion. One study tested 18-, 20-, and 22-gauge needles with bevel facing up, down, and sideways using 2 penetration techniques.[34] The bevel-up position induced the least fragmentation, while bevel down with needles >22 gauge yielded the most. Consistent with other studies,[35] penetration of rubber stoppers on vials with a blunt needle has a greater incidence of fragmentation and "coring" (parts of the rubber stopper enter the vial).[34] To minimize the risk of coring, it is advised to push through the middle of the bullseye design on the rubber stopper with a 45° angle and bevel up while smoothly and simultaneously rotating the needle to a 90° angle after exiting the underside of the stopper.[34] To prevent a vacuum, before aspirating the natalizumab solution, one should inject a volume of air equal to the volume of solution to be aspirated into the airspace. Inverting the vial and confirming that the tip of the needle is in the fluid space while slowly withdrawing the solution will minimize the risk of air bubbles.

Administration

Storage/stability requirements and administration have been detailed previously.[34] Briefly, after dilution, the prepared natalizumab solution should be infused immediately or refrigerated at 2°C to 8°C (36° to 46°F), but not frozen, and infused within 8 hours of preparation. Prior to infusion, diluted solution stored at 2°C to 8°C should be removed from refrigeration and allowed to warm slowly to room temperature; warming may take approximately 1 to 2 hours. Accelerated warming methods should not be used. The infusion of natalizumab should be done at a fixed rate over 1 hour. Natalizumab should never be administered as a bolus injection or IV push. Additionally, natalizumab should not be mixed with any other medication.[33]

Reported saline shortages have prompted discussions for best practices regarding postinfusion tubing line flush to ensure the patient receives the entire 300-mg dose. Depending on the length and type of tubing, there could be approximately 20 to 30 mL of diluted medication remaining in the tubing. It is important to replace the completed bag with a new bag of at least 20 mL of 0.9% sodium chloride (50- or 100-mL prefilled bags are typically used) and run at the same rate as the medication administration; alternatively, draining the tubing by gravity as much as possible will result in less residual volume being discarded. This should be followed by flushing the vascular access device per standard protocol (typically 5 mL for peripheral and 10 mL for central access devices).

Monitoring for Infusion-Related Reactions

As with any infused agent, infusion-related reactions, defined as any event occurring within 2 hours after the

start of the infusion, may occur. Natalizumab infusions are generally well tolerated, with the most common infusion reaction being headache, at an incidence of 5% with natalizumab, compared to 3% with placebo, as reported in the phase 3 AFFIRM study.[7] Serious infusion-related hypersensitivity reactions in natalizumab patients have been reported at rates <1% in postmarketing studies.[10,36] Symptoms associated with hypersensitivity reactions can include urticaria, dizziness, fever, rash, rigors, pruritus, nausea, flushing, hypotension, dyspnea, and chest pain.[5] A recent analysis of more than 3000 natalizumab-treated MS patients found that the incidence of infusion-related reactions and infusion-related hypersensitivity reactions decreased with natalizumab exposure duration.[37]

The current guidance in the US prescribing information is to observe patients during the infusion and for 1 hour postinfusion for the first 12 infusions.[5] Upon the first observation of any signs or symptoms consistent with a hypersensitivity-type reaction, the infusion should be promptly discontinued, and the appropriate therapy for the hypersensitivity-type reaction should be initiated. The severity of the reaction and the presence of multiple symptoms should be considered when making a treatment decision. The use of antihistamines is a generally accepted practice for mild hypersensitivity reactions, such as mild urticaria.[33] For emergency treatment, it is imperative to maintain vascular access and fluid support and to notify the treating clinician.[33] Patients who experience a hypersensitivity reaction should not be retreated with natalizumab. For patients who have received 12 infusions without evidence of a hypersensitivity reaction, clinical judgment should dictate the level of postinfusion observation for the 13th and subsequent infusions.[5]

Best practice may include posting the emergency protocol(s) of the facility in a prominent place where the infusions occur. Patients should be educated regarding signs of immediate and delayed hypersensitivity reactions and the importance of contacting emergency medical services if they experience any of the symptoms. Considerations for administering natalizumab in various practice settings have previously been discussed.[33]

Immunogenicity

As with all therapeutic proteins, patients receiving natalizumab may develop antibodies against the drug. In the AFFIRM clinical trial, 6% of natalizumab-treated patients were persistently positive for anti-natalizumab antibodies (meaning that they tested positive for antinatalizumab antibodies at 2 or more time points at least 6 weeks apart).[38] The majority of these patients developed detectable antibodies by 12 weeks.[5,38]

Persistent antibody positivity has been associated with the loss of clinical efficacy; this observation is supported by the finding that the mean serum natalizumab concentration was substantially lower in persistently antibody-positive patients compared with antibody-negative patients.[38] Persistent antibody positivity has also been associated with a higher incidence of infusion-related reactions, including hypersensitivity reactions.[38] Therefore, antinatalizumab antibody testing should be considered in natalizumab-treated patients with a suboptimal response or with persistent infusion-related adverse events.

Pregnancy and Lactation

The decision to use natalizumab during pregnancy depends on the individual patient and should be determined jointly by the patient and clinician. As commonly seen in phase 3 MS DMT clinical trials, women who were pregnant or planning to become pregnant were excluded from the natalizumab phase 3 AFFIRM trial.[7] As natalizumab is often used in patients with MS whose disease activity pretreatment was high, the potential risk to the mother must be considered and balanced against the risk to the fetus. There have been 2 independent observational studies conducted that compared maternal and fetal outcomes according to natalizumab gestational exposure. The results showed that longer natalizumab gestational exposure was associated with fewer maternal relapses, but more newborns were born with hematological anomalies (HAs).[39,40] One of the studies had follow-up blood counts for 12 of the 15 newborns who had HAs. The HAs were reversible during the first month postpartum in 9 of these newborns, and only 1 newborn received treatment.[40]

For patients with historically highly active disease who decide to continue natalizumab during pregnancy, some sources suggest extending the dosing interval to every 6 to 8 weeks until 34 weeks' gestation.[41,42] Following delivery, it is recommended to resume natalizumab treatment early (in the first 4 weeks after birth) to minimize the risk of return of disease activity. The neonate should also be evaluated for hematological abnormalities.[41-43]

As with other DMTs, lactation studies on natalizumab-treated women are limited.[42] However, natalizumab has been shown to be detected in the milk of lactating women being treated with natalizumab.[5] While some suggest that natalizumab is probably compatible with breastfeeding,[42] discussions with the patient should include current guidance, as well as current unknowns.

Use With Vaccination

Natalizumab treatment does not deplete lymphocytes but instead retains them in the periphery, thereby leaving the peripheral immune system intact.[5] Like many other DMTs, the number of studies examining the impact of natalizumab treatment on the ability of a patient to mount an adequate immune response to a specific vaccine, with the exception of COVID-19 vaccines, is somewhat limited. In a randomized, open-label study of 60 patients with relapsing MS, no significant difference in the immune response to the tetanus toxoid vaccine was observed in patients who were treated with natalizumab (n = 30) for 6 months compared with an untreated control group (n = 30).[44] Data from

multiple studies have shown that natalizumab-treated MS patients were able to mount an immune response to COVID-19 vaccines comparable to that of untreated MS patients and/or healthy controls.[45-49] For general guidance regarding vaccinations in MS patients, please refer to the National MS Society website, as well as the American Academy of Neurology published guideline.[50,51]

CONCLUSIONS

Infusion nurses are at the front line of care for patients with MS receiving infusible DMTs like natalizumab. Key responsibilities include the administration of natalizumab, as well as patient monitoring, education, and support. A thorough understanding of the safety profile of natalizumab, including PML risk mitigation strategies, as well as the recognition of clinical signs/symptoms suggestive of PML and hypersensitivity reactions, will enable infusion nurses to ensure that natalizumab-treated patients receive optimal care.

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APPENDIX 1

Practical Guidelines for Natalizumab Preparation, Administration, and Monitoring

Preparation

1. Review and complete the preinfusion checklist with the patient. Once it is confirmed that the patient is authorized to receive the infusion, follow institution's policy and procedure for intravenous (IV) starts.
2. Wash hands.
3. Clean port of 100-mL IV bag of 0.9% sodium chloride (normal saline) with alcohol wipe.
4. Inspect the natalizumab vial for particulate material and discoloration prior to dilution. If present, the vial must not be used.
5. Remove cap from natalizumab vial, and clean rubber stopper with alcohol wipe.
6. Using 20-mL syringe with 18- to 20-gauge sterile needle, push ≈15 mL of air into air space of inverted natalizumab vial. Do not bubble air through drug solution.
7. Withdraw 15 mL natalizumab concentrate from vial.
8. Discard needle and, via new 18- to 20-gauge needle, gently inject natalizumab concentrate into IV bag medication port diaphragm. No IV diluents other than 0.9% sodium chloride (normal saline) should be used to prepare natalizumab dosing solution.
9. Diluted drug in IV bag should be gently inverted to mix completely. Do not shake.
10. After dilution, inspect the solution to ensure no particulate prior to administration. If not infused immediately, store at 2° to 8°C (36°–46°F) and infuse within 8 hours. Allow to warm to room temperature before infusing. Do not freeze.
11. Remove and dispose of needle, syringe, and vial in compliance with Occupational Safety and Health Administration standards and facility protocol.
12. Label IV bag with patient's name, drug, dose, date, and time. Initial.

Administration

1. Wash hands.
2. Use an alcohol wipe or alcohol/chlorhexidine wipe to scrub the hub of the catheter prior to infusion.
3. Flush and prime tubing system with diluted drug in bag (a few milliliters of diluted drug may be lost in priming process). Connect to IV catheter.
4. Infuse diluted drug in IV over ≈1 hour (rate ≈2 mL/min). Do NOT administer as an IV push or bolus infusion. Also, other medications should not be injected into infusion set side ports or mixed with natalizumab.
5. Once entire bag of diluted drug is empty, replace with a 50- to 100-mL bag of 0.9% sodium chloride (normal saline). Infuse an additional 20 mL of saline into patient to flush IV line (rate: ≈2 mL/min).
6. After infusion is complete, dispose of materials properly.

Monitoring During Infusion

1. Check IV infusion site for redness, warmth, pain, swelling, or leakage.
2. Ask patient whether they are experiencing infusion-site itching or discomfort.
3. Promptly discontinue the infusion upon the first observation of any signs or symptoms consistent with a hypersensitivity-type reaction, which can include urticaria, dizziness, fever, rash, rigors, pruritus, nausea, flushing, hypotension, dyspnea, and chest pain, and initiate appropriate therapy.

Monitoring Postinfusion

1. Postinfusion, for the first 12 infusions, observe the patient for 1 hour after the infusion is complete for any signs or symptoms suggestive of a hypersensitivity-like reaction.
2. For patients who have received 12 infusions without evidence of a hypersensitivity reaction, observe the patient postinfusion for the 13th and subsequent infusions according to clinical judgment.

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