CLINICAL THERAPEUTICS

Natalizumab for Multiple Sclerosis

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This Journal *feature begins with a case vignette that includes a therapeutic recommendation. A discussion of the clinical problem and the mechanism of benefit of this form of therapy follows. Major clinical studies, the clinical use of this therapy, and potential adverse effects are reviewed. Relevant formal guidelines, if they exist, are presented. The article ends with the author's clinical recommendations.*

A 30-year-old woman was evaluated for consideration of treatment options for multiple sclerosis. Two years earlier she had reported having vertigo. The diagnosis of multiple sclerosis was confirmed by clinical evaluation, examination of cerebrospinal fluid, and magnetic resonance imaging (MRI). Injections with interferon beta had been discontinued because of worsening depression (which had preceded the onset of multiple sclerosis). Despite treatment with glatiramer acetate injections and bimonthly intravenous administration of methylprednisolone, she had three episodes of acute neurologic deterioration, with motor and cerebellar involvement, and incomplete recovery between the attacks. Neurologic examination showed mild ocular and limb dysmetria, weakness of the right side, and sensory loss below the midthorax. She was referred to a multiple sclerosis center for possible treatment with natalizumab.

THE CLINICAL PROBLEM

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Multiple sclerosis is an acquired inflammatory demyelinating disease of the central nervous system that is regarded as the foremost cause of nontraumatic neurologic disability in adults in North America, with a prevalence of approximately 1 case per 1000 population and a predominance in women (female:male ratio, 2:1). The mean age at onset is 30 years. Although multiple sclerosis is notoriously heterogeneous, in 85% of patients it begins with episodic, largely reversible neurologic dysfunction, in a pattern termed relapsing–remitting multiple sclerosis. In 75% of those patients, the disease advances over time to steady, irreversible worsening, designated secondary–progressive multiple sclerosis. Less than 5% of patients have very severe disability (fulminant multiple sclerosis) within the first 5 years after onset, and 10 to 20% of patients remain unimpaired without therapy (benign multiple sclerosis) for 20 years.

Multiple sclerosis has a modest effect on longevity but takes a heavy toll on quality of life. Natural history studies show 50% of patients reaching disability milestones as follows: loss of employment (10 years after diagnosis), use of assistive walking devices (15 years), inability to walk (25 years).[1] Whether current disease-modifying drugs alter this prognostic formulation is unknown. The costs of multiple sclerosis in the United States and Europe are similar, at about $47,000 per patient per year.[2,3] Total yearly costs related to multiple sclerosis in the United States exceed $14 billion.

PATHOPHYSIOLOGY AND EFFECT OF THERAPY

A composite working hypothesis of the pathogenesis of multiple sclerosis is based on epidemiologic and genetic data and reasoning by analogy from animal models, tissue studies, and imaging.[4,5] Inflammatory tissue injury sets the stage for sustained neurodegeneration such that the pathophysiology of the disease plays out in concert

with advancing clinical manifestations (Table 1). Initiating events have not been identified, but one theory holds that in a genetically susceptible host, exposure to any one of many common agents, including the Epstein–Barr virus, can activate or dysregulate T cells that recognize myelin protein antigens.[8-11]

The clinical onset of multiple sclerosis is thought to occur more than a decade after the initiating event. This phase of latency terminates with the first demyelinating episode, termed clinically isolated syndrome, which is believed to be triggered in many cases by nonspecific immune activation brought on by a viral or bacterial illness. The formal diagnosis of multiple sclerosis requires a second demyelinating episode, the appearance of new, typical lesions on MRI, or unequivocal evidence of one or more previous demyelinating episodes. Any of these events, in combination with a demyelinating episode that prompts neurologic evaluation, leads to a diagnosis of relapsing–remitting multiple sclerosis.[12-14]

The demyelinating lesions of multiple sclerosis contain mononuclear leukocyte infiltrates that are intimately involved in tissue injury.[15] The migration of leukocytes out of the vasculature and into organ parenchyma requires an interaction between adhesion molecules on the leukocytes and complementary ligands on the surface of vascular endothelial cells. In multiple sclerosis, the interaction between $\alpha_4\beta_1$ integrin on T cells and counter-receptors on the vascular endothelium plays a central role[16,17] (Fig. 1).

Leukocyte integrins are heterodimeric glycoproteins consisting of an α chain and a β chain. Natalizumab contains humanized neutralizing IgG4κ monoclonal antibodies against leukocyte α_4 integrins, which include $\alpha_4\beta_7$ and $\alpha_4\beta_1$, found on lymphocytes and monocytes. By blocking α_4 integrins, natalizumab abrogates the movement of mononuclear leukocytes to the small intestine (which requires $\alpha_4\beta_7$) or to other inflamed tissues, including the central nervous system, where $\alpha_4\beta_1$ is essential.[16,18] The ability of natalizumab to suppress leukocyte entry into the central nervous system is what mediates its therapeutic benefit for multiple sclerosis[15,19,20] (Fig. 1).

CLINICAL EVIDENCE

The use of natalizumab to treat multiple sclerosis was evaluated in two phase 3 clinical trials. Both trials involved patients with relapsing–remit-

Table 1. Evolution of Multiple Sclerosis in Patients Who Present with Relapsing–Remitting Symptoms Followed by a Chronic–Progressive Phase.*

Feature	Stage 1: Initiation	Stage 2: Latency	Stage 3: Onset	Stage 4A: Inflammation	Stage 4B–5A: Transition	Stage 5B: Neurodegeneration
Disease-modifying therapies	None	None	Antiinflammatory therapies effective	Antiinflammatory therapies effective	Antiinflammatory therapies less effective	None
Clinical events	None	None	Single episode of inflammatory demyelination	Intermittent symptomatic attacks, often with satisfactory recovery; stable neurologic baseline	Unstable neurologic status; incomplete recovery from some attacks	Steady progression occasionally punctuated by attacks; variable periods of stability without marked improvement
Proposed pathogenesis†	Activation of autoreactive lymphocytes; molecular mimicry superantigen; altered lymphocyte physiology due to Epstein–Barr virus	Stochastic intrathecal accumulation of inflammatory cells	Inflammatory demyelination triggered by systemic infection (e.g., upper respiratory)	Recurrent bouts of demyelination with axonal injury; cortical pathology; variable repair	Axonal-injury threshold reached, with failure of repair and compensation‡	Widespread glial activation; cortical disease; ongoing axonal degeneration; meningeal inflammation
Age (yr)						
Typical	13–15	15–30	30	30–45	45–55	45–75
Range	5–20	10–50	2–50	<70		

* Multiple sclerosis follows this five-stage pattern in approximately 60% of affected patients.
† The proposed pathogenic events are derived from epidemiologic and pathological studies as well as animal models.
‡ Information on the concept of threshold is available in Hauser et al.[6] and Frohman et al.[7]

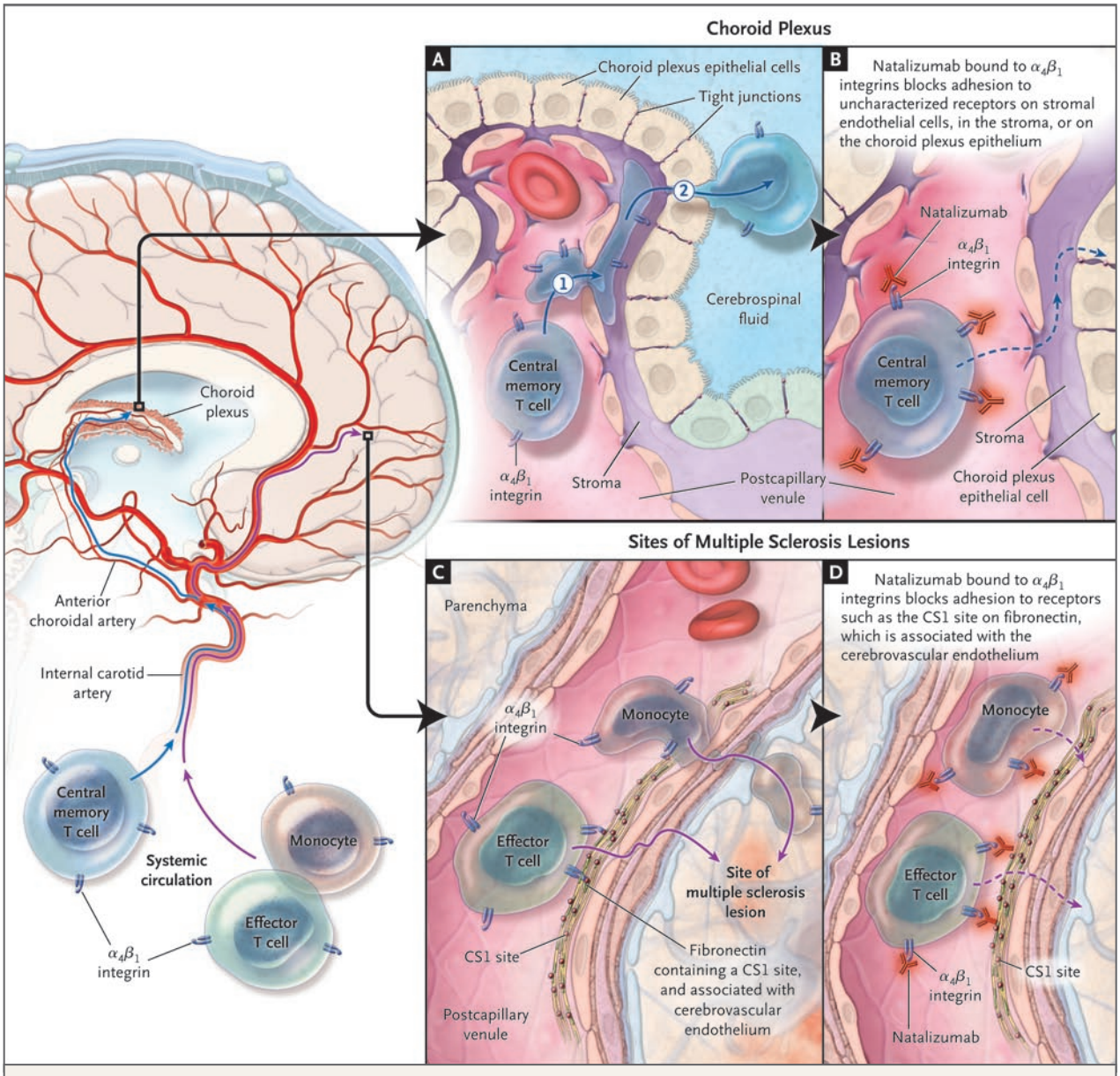

Figure 1. Effects of Natalizumab on the Movement of Mononuclear Cells to the Central Nervous System.

Several subtypes of mononuclear cells (central memory T cells, effector memory T cells, and activated monocytes) enter the central nervous system through the internal carotid artery and travel to distinct compartments by different routes. Central memory T cells proceed through the anterior choroidal artery into the cerebrospinal fluid (CSF) and through the choroid plexus in two stages. Initial extravasation occurs through the choroid plexus postcapillary venules into the stroma, and cells then migrate through the tight junctions of the choroid plexus epithelium into the CSF. These CSF central memory T cells carry out immune surveillance of the central nervous system. Activated effector memory T cells and monocytes travel through the intracranial circulation and extravasate within inflamed multiple sclerosis lesions, across the blood–brain barrier. These cells mediate pathogenic inflammation in multiple sclerosis lesions. All these cell types express $\alpha_4\beta_1$ integrins on the cell surface; transport both to the CSF and into the lesions of multiple sclerosis is suppressed when natalizumab binds and inactivates the integrin molecule. The endothelial binding partner for $\alpha_4\beta_1$ integrin has not been conclusively identified, either in the choroid plexus or in the inflamed vessels of multiple sclerosis lesions. (Updated September 14, 2007.)

ting multiple sclerosis and excluded patients with primary or secondary progressive forms of the disease.

In the first study, a monotherapy trial, 942 patients were randomly assigned to receive natalizumab or placebo by intravenous infusion every 4 weeks for 2 years.[21] A neurologist who was unaware of the treatment-group assignments

evaluated relapses and the progression of disability, using the Expanded Disability Status Scale. MRI brain scans were obtained at baseline, 1 year, and 2 years. According to an intention-to-treat analysis, treatment with natalizumab reduced the cumulative probability of sustained disability progression from 29 to 17% (P<0.001; number needed to treat, 9). The likelihood of remaining relapse-free was increased from 41 to 67% after 2 years (number needed to treat, 4). Natalizumab reduced the number of new gadolinium-enhancing lesions on MRI at year 2 by 92% (P<0.001). A significant effect of natalizumab on gadolinium-enhancing lesions was demonstrable after 6 weeks of therapy.

In the second study, a 2-year phase 3 trial of similar design, natalizumab or placebo was added to interferon beta for patients who had had at least one relapse during 12 consecutive months of previous treatment with interferon beta.[22] The study, which enrolled 1171 subjects, showed that treatment with both drugs was more effective than treatment with interferon beta alone: patients receiving combination therapy were less likely to have sustained progression (23% vs. 29%; number needed to treat, 17), were more likely to remain relapse-free (61% vs. 37%; number needed to treat, 5), and had an 89% reduction in gadolinium-enhancing lesions on MRI. The study ended a month early, however, because of the occurrence of progressive multifocal leukoencephalopathy (PML) in two patients who received natalizumab in addition to interferon beta.

CLINICAL USE

Natalizumab was approved for treatment of relapsing–remitting multiple sclerosis in November 2004 on the basis of an expedited review of the 1-year results of the two trials. However, clinical trials and distribution of natalizumab were suspended in February 2005 after PML was detected in three trial participants. Retrospective surveillance of more than 3700 subjects failed to disclose additional cases of PML, and natalizumab was reintroduced in July 2006 as monotherapy for relapsing forms of multiple sclerosis, with a black-box warning about PML. Natalizumab was re-released in a restricted-distribution format, defined under the TOUCH Prescribing Program. The prescription of natalizumab is now restricted to pharmacies and infusion centers participating in the TOUCH program, which incorporates mandatory education, monitoring, and reporting requirements. (More information is available at www.fda.gov/cder/drug/infopage/natalizumab/RiskMAP.pdf.)

Consensus principles for the management of multiple sclerosis and the results of the natalizumab clinical trials provide guidance for the use of natalizumab in the treatment of multiple sclerosis. First, not all patients with multiple sclerosis require active medical therapy.[23] Active treatment is appropriate for patients with relapsing–remitting multiple sclerosis who have central nervous system inflammation in the form of relapses or disease activity evident on MRI scans. Second, the vast majority of patients with newly diagnosed multiple sclerosis are not candidates for treatment with natalizumab because their long-term prognosis is unknown at the time of presentation and because a favorable long-term course remains possible.[24] Instead, patients with active, newly diagnosed multiple sclerosis should begin therapy with one of the two approved first-line agents (interferon beta or glatiramer acetate), which may provide satisfactory control of disease activity in some cases.[6] Although natalizumab appears to be more effective than either interferon beta or glatiramer acetate,[25] no direct comparisons have been performed, and conclusions drawn from intertrial comparisons can be misleading.

When therapy with interferon beta or glatiramer acetate is not successful, the patient should be carefully evaluated to identify possible reasons (which may include infection, the presence of neutralizing antibodies to interferon beta, or nonadherence).[26,27] Failure of first-line medications can be addressed by switching to an alternative agent, although very little information regarding the effectiveness of this strategy is available and physician behaviors vary widely. For patients with rapidly worsening inflammatory relapsing–remitting multiple sclerosis, there are several therapeutic options, including immunosuppression with cyclophosphamide or mitoxantrone, scheduled pulse therapy with intravenous corticosteroids, and treatment with natalizumab.[12,28-31]

Patients with progressive multiple sclerosis are not candidates for natalizumab therapy at present. These forms of multiple sclerosis were criteria for exclusion from clinical trials,[21,23] and their pathogenesis appears to be different from that of relapsing–remitting multiple sclerosis.[7,32,33]

Specific contraindications to natalizumab therapy include hypersensitivity to the drug and a history of PML. However, conditions that com-

promise immunity (including a history of hematologic cancer and rheumatic disease[34,35]) should provoke reconsideration of natalizumab therapy. Natalizumab should not be administered if the patient has taken immunosuppressive agents (mitoxantrone, cyclophosphamide, mycophenolate mofetil, methotrexate, or azathioprine, among others) within the previous 3 months. The leukocyte and differential counts should be within normal limits.

Before therapy with natalizumab is initiated, the diagnosis of multiple sclerosis must be completely secure. Although this imperative applies generally to all forms of therapy for multiple sclerosis, in the case of natalizumab it is heavily underscored by the fact that one patient in whom fatal PML developed during a clinical trial did not have the neuropathological changes of multiple sclerosis at autopsy, and the accuracy of the diagnosis in this patient is now considered dubious.[36] Numerous medical conditions can mimic multiple sclerosis and should be excluded with the use of contemporary clinical, laboratory, and imaging criteria.[37,38]

Treatment takes place at an infusion center, where natalizumab is administered through a peripheral vein once a month at a dose of 300 mg. Infusions are given over the course of an hour, with an additional hour of postinfusion observation and the presence of any personnel and resources needed to treat adverse reactions. TOUCH program guidelines mandate evaluation of patients before infusions 4, 7, and 13 and every 6 months thereafter, according to the practitioner's individual preference. In the clinical trials, the onset of a therapeutic effect occurred at 6 weeks. It seems evident that a change in therapy should be strongly considered if patients have ongoing disease activity (relapses or new abnormalities on MRI studies) after 6 months of treatment. Because natalizumab is approved only for monotherapy, adding a medication is not an option.

Patients receiving natalizumab should not become pregnant. Rodents in which α_4 integrins have been eliminated through gene targeting or that received α_4 integrin antagonists die in early embryonic stages,[39] a finding that suggests that the α_4 integrins may be essential for embryonic development.

Monitoring for PML is essential in patients receiving natalizumab. The TOUCH program requires monthly evaluation by medical professionals at the infusion center, with specific attention to symptoms that are consistent with PML, including altered mental status, hemianopia, aphasia, and seizure. If PML is suspected, natalizumab therapy must be suspended pending evaluation. To differentiate attacks of multiple sclerosis from the onset of PML, questioning is focused on the distinct features of multiple sclerosis that are virtually never observed in PML. These include an abrupt onset of neurologic symptoms, involvement of the optic nerve or spinal cord, and rapid regression of symptoms after the administration of corticosteroids. Clinical differentiation between multiple sclerosis and PML, which may rely on findings from serial MRI studies and examination of cerebrospinal fluid as well as neurologic evaluation, requires the expertise of a practitioner with substantial experience in diagnosing central nervous system demyelinating disorders. Also, given the postrelease occurrence of herpesvirus infections of the central nervous system in two patients, clinical surveillance for viral infections of the central nervous system, and for herpesvirus infections in particular, is warranted.

The yearly wholesale cost of natalizumab is $28,400 (for 13 doses). Additional costs for infusion services and for visits or tests associated with monitoring vary considerably according to the medical care setting and geographic location.

ADVERSE EFFECTS

The most important adverse effect of natalizumab therapy is the development of PML, a rare, serious opportunistic infection of the oligodendrocytes by the JC polyomavirus.[20,40] PML developed in two natalizumab recipients in the multiple sclerosis clinical trials and in one such recipient in a Crohn's disease clinical trial; two of these patients died of the disease, and the surviving patient was severely disabled.[41,42] Both patients with multiple sclerosis in whom PML developed were also receiving interferon beta.[22] A retrospective review showed that the estimated risk of PML in patients treated with natalizumab was 1 case per 1000 patients in 18 months.[40] The mechanism of natalizumab's involvement in the pathogenesis of PML, however, remains uncertain.[43]

In the multiple sclerosis clinical trials, infectious complications of natalizumab other than PML were infrequent. There was a small excess of herpes infections, pneumonia, and urinary tract

infection in patients taking natalizumab, but there was only one noteworthy infection (cryptosporidial gastroenteritis).[21,22] There were no other opportunistic infections, and there was no increase in cases of cancer. Postrelease monitoring disclosed one case of fatal herpesvirus encephalitis and one nonfatal case of herpesvirus meningitis. There were no cases of disseminated herpes zoster.

Natalizumab infusions were complicated by serious hypersensitivity reactions, including fever, rigors, and anaphylaxis, in less than 1% of recipients, with less-serious infusion reactions (urticaria or rash) in about 4% of patients. These reactions usually occurred within 2 hours after the start of the infusion, most often after the second or third infusion.

Persistent neutralizing antibodies to natalizumab developed in approximately 6% of patients. Patients with infusion reactions were more likely to have persistent neutralizing antibodies to natalizumab on subsequent testing.[44] Persistent neutralizing antibodies abrogated the efficacy of natalizumab, resulting in clinical and radiographic disease activity equivalent to that seen in the placebo group thereafter.[22]

Patients receiving natalizumab had altered blood counts, with increased lymphocytes, monocytes, eosinophils, and basophils and occasional detection of nucleated erythrocytes. These changes are related to blockade of α_4 integrins, causing the release of bone marrow myeloid and lymphoid cells and possibly also reflecting reduced numbers of leukocytes moving from the bloodstream into tissues, including the central nervous system.[16,19,45-47]

AREAS OF UNCERTAINTY

At present, decisions about appropriate use of natalizumab must be made in an atmosphere of doubt and ambiguity, tempered by the likelihood that forthcoming information will resolve important outstanding questions. Many of the unresolved issues in the use of natalizumab for multiple sclerosis involve the risk of PML. A data registry mandated by the TOUCH program may help to address unanswered questions. The single most important unanswered near-term questions are whether PML will occur with natalizumab monotherapy and, if so, at what frequency. It is also unclear whether the risk of PML will increase, decrease, or remain constant with prolonged therapy. This question is particularly salient, because in most patients with multiple sclerosis, disease activity is suppressed for a period of 10 to 20 years — 12 to 24 months of treatment with natalizumab will not address the medical needs of most patients. To aid in the selection of the best candidates for natalizumab therapy, identification of host factors that increase susceptibility to PML would be useful. It will also be important to define indicators of impending PML that will allow for discontinuation of treatment at the earliest possible time. No therapeutic interventions (other than discontinuation of natalizumab or another immunosuppressive treatment) are beneficial in treating PML.[48]

The optimal duration of treatment with natalizumab is unknown. Whether a clinical benefit will be sustained beyond 2 years remains uncertain. Alternatively, 2 years of natalizumab might be used as induction therapy; subsequent use of current first-line agents, with their better-known safety profiles, could then be appropriate. The potential role of natalizumab therapy in treating forms of multiple sclerosis other than relapsing–remitting disease (e.g., progressive multiple sclerosis) has not been explored, although given the distinct pathogenesis of other forms of the disease, it is unclear whether a beneficial effect could be expected. Finally, head-to-head comparisons of natalizumab with other available therapies would be invaluable for practitioners and patients.

GUIDELINES

Natalizumab is approved by the Food and Drug Administration for treatment of patients with relapsing forms of multiple sclerosis, but no formal recommendations for its appropriate use have been provided by professional societies or expert panels.[49,50] At present, natalizumab should be suggested only for patients who meet the following criteria: first, recent inflammatory disease activity (one or more relapses within the past year, with or without the presence of gadolinium-enhancing lesions on MRI), and second, documented evidence that alternative medications have been ineffective or poorly tolerated. Patients beginning treatment with natalizumab should have taken no immunosuppressive medications in the preceding 3 months, they should have no condition that compromises cell-mediated immunity (including coexisting rheumatologic or hematologic disorders), and their leukocyte counts, at minimum, should be normal.

They should also be able to provide informed consent and to comply with the requirements of the mandatory monitoring program.

RECOMMENDATIONS

The circumstances of the patient in the vignette warrant discussion of therapy with natalizumab. She has received a diagnosis of multiple sclerosis, could not tolerate interferon beta, and did not have a response to glatiramer acetate and intravenous methylprednisolone. Ominous prognostic indicators are present, including frequent attacks with incomplete recovery as well as early motor, spinal, and cerebellar involvement.

Her neurologic assessment should be carefully reviewed to make sure that she meets stringent criteria for a diagnosis of relapsing–remitting multiple sclerosis, including dissemination of lesions both in time and space, typical changes in cerebrospinal fluid, and exclusion of alternative explanations for her inflammatory central nervous system disease. Provided that these criteria are satisfied, I would discuss with her the options of treatment with either a cytotoxic immunosuppressive agent or natalizumab, considering the potential advantages and risks of each. Should she choose natalizumab, it would be necessary to enroll her in the TOUCH program to monitor her therapy and clinical course.

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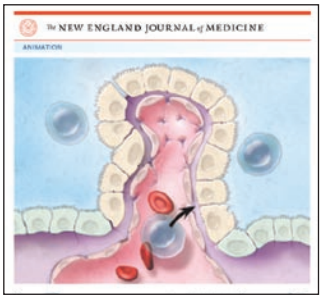

An animated illustration showing the pathophysiology of multiple sclerosis and the action of natalizumab is available with the full text of this article at www.nejm.org.

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