PHARMACOLOGY VIGNETTE

Natalizumab (Tysabri)

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SUMMARY: Natalizumab is a humanized IgG4κ monoclonal antibody that is a selective adhesion molecule inhibitor, which prevents adhesion of leukocytes to endothelial cells. It is the first monoclonal antibody approved by the FDA for the treatment of relapsing-remitting MS. This article will review the mechanism of action and clinical role of this agent.

ABBREVIATIONS: FDA = US Food and Drug Administration; FLAIR = fluid-attenuated inversion recovery; FSE = fast spin-echo; IgG = immunoglobulin G; MAdCAM-1 = mucosal adressin cell adhesion molecule; MS = multiple sclerosis; PML = progressive multifocal leukoencephalopathy; TOUCH = Tysabri Outreach Unified Commitment to Health; VCAM -1 = vascular cell adhesion molecule-1

Natalizumab (Tysabri; Biogen Idec, Cambridge, Massachusetts and Elan Pharmaceuticals, Dublin, Ireland) was the first FDA-approved monoclonal antibody for the treatment of MS. Natalizumab received FDA approval in 2004 for treatment of relapsing-remitting MS based on the AFFIRM and SENTINEL phase 3 clinical trials.[1,2] More recently, the indications for natalizumab were expanded to include Crohn disease.[3-5] In 2005, natalizumab was removed from the market following cases of PML but was reintroduced by the FDA with a mandatory surveillance program in 2006 called TOUCH (Biogen).[6]

Proposed Mechanism of Action

Natalizumab is a humanized monoclonal IgG4κ antibody that selectively binds to the α4-integrin component of adhesion molecules found on lymphocytes, monocytes, and eosinophils.[7] α4-integrin is a subunit of the leukocyte adhesion molecules $\alpha4\beta1$ and $\alpha4\beta7$. In 1991, Yednock et al[8] showed that targeting α4-integrin could prevent the development of demyelinating lesions in a mouse model of MS, elucidating the therapeutic potential for this medication.[9] Natalizumab inhibits the interaction of $\alpha4\beta1$ with VCAM-1 and of $\alpha4\beta7$ with MAdCAM-1.[10] VCAM-1 and MAdCAM-1 are found on endothelial cells and interact with $\alpha4\beta1$ and $\alpha4\beta7$ on leukocytes for firm adherence of leukocytes to endothelial cells, a requisite step for their extravasation into inflamed tissue (Fig 1).[11] Natalizumab prevents migration of autoreactive leukocytes out of blood vessels into target organs by blocking the adhesion to endothelial cells of the α4-integrin component of adhesion molecules on leukocytes, inhibiting inflammation (Fig 2). Because VCAM-1 is expressed on inflamed cerebrovascular endothelial cells, $\alpha4\beta1$ is believed to be the critical target of natalizumab in preventing leukocyte migration into the central nervous system in MS. In contrast, both VCAM-1 and MAdCAM-1 are upregulated on intestinal endothelium in Crohn disease. The efficacy of natalizumab in Crohn disease very likely is due to blockade of leukocyte adhesion factors $\alpha4\beta1$ and $\alpha4\beta7$ in tandem.[4,7,10]

Clinical Indications

Natalizumab is approved for treatment of relapsing-remitting MS and Crohn disease. It is generally reserved for patients who fail first-line therapies (Figs 3 and 4).[12] It must be given in conjunction with the TOUCH program, which is a national risk-minimization program designed to "minimize the risk of PML, minimize death and disability due to PML, and promote informed risk-benefit decisions regarding Natalizumab use."[6] This drug is being investigated for use in ulcerative colitis.

Administration

Natalizumab is administered at specialized infusion centers enrolled in the TOUCH program for 1 hour with 1-hour monitoring. The TOUCH program also mandates regular appointments and follow-ups to monitor for signs of PML. The half-life is 11 days after 6 months of therapy.[13]

Side Effects

Reported serious side effects include the following:

- Neutralizing antibody development: occurs in $\leq$10% of patients.[1,4,5,14]
- Transfusion reaction/hypersensitivity: transfusion reactions ranging in severity from minor to anaphylaxis have been reported.[1,2,12] These reactions are more common in patients with neutralizing antibodies.[5]
- PML: a serious central nervous system infection due to JC virus, cases have been reported in patients with MS and Crohn disease.[15] Natalizumab is recommended for use as a monotherapy in MS[12] and Crohn disease to minimize risk.
- Hepatotoxicity: clinically significant liver injury has been reported in 6 individuals without long-term liver failure.[16]
- Opportunistic infection: viral encephalitis, cytomegalovirus, aspergillosis, cryptosporidium diarrhea, pneumocystis pneumonia, mycobacterium avium intracellulare, and Burkholderia cepacia pneumonia have been reported.[17]
- Malignant melanoma: reports of malignant melanoma following therapy.[18,19]

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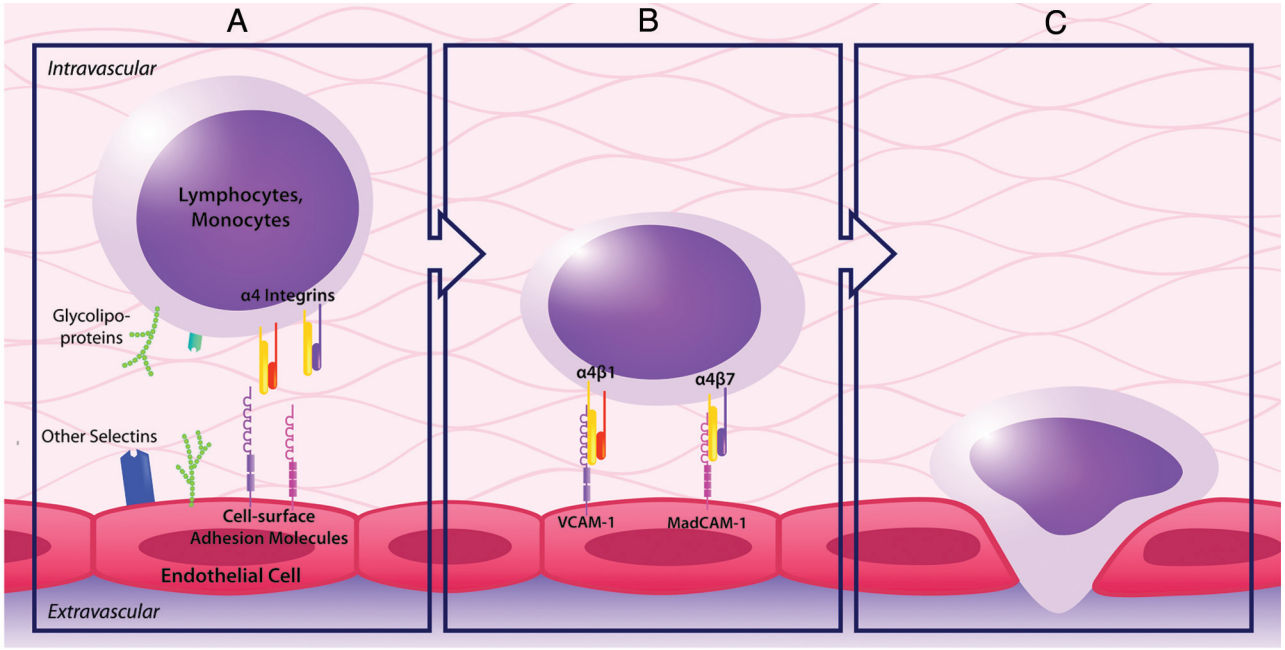

Fig 1. The normal process of leukocyte migration out of blood vessels into tissue involves interactions between leukocytes and endothelial cells including rolling (*A*), adhesion (*B*), and extravasation (*C*). The adhesion molecules $\alpha4\beta1$ and $\alpha4\beta7$ found on leukocytes are integral in the adhesion process to endothelial cells.

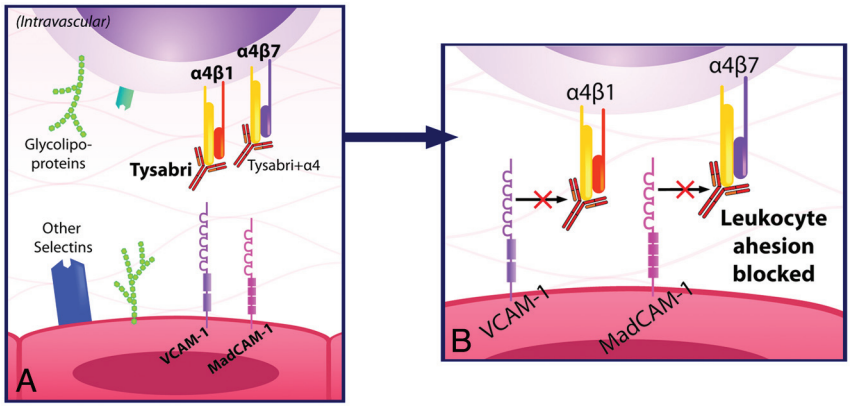

Fig 2. *A,* Natalizumab blocks the adhesion of leukocytes to endothelial cells by blocking the interaction of the $\alpha4$-integrin subunit of $\alpha4\beta1$ with VCAM-1 and of $\alpha4\beta7$ with mucosal MAdCAM-1. *B,* This prevents autoreactive leukocytes from exiting blood vessels and entering target organs to cause inflammation.

Economic Issues

Natalizumab is given at 300 mg intravenously every 4 weeks for Crohn disease and MS. The cost is roughly $2800 per vial (300 mg) with an annual cost of $34,000. This is covered by most insurance companies.

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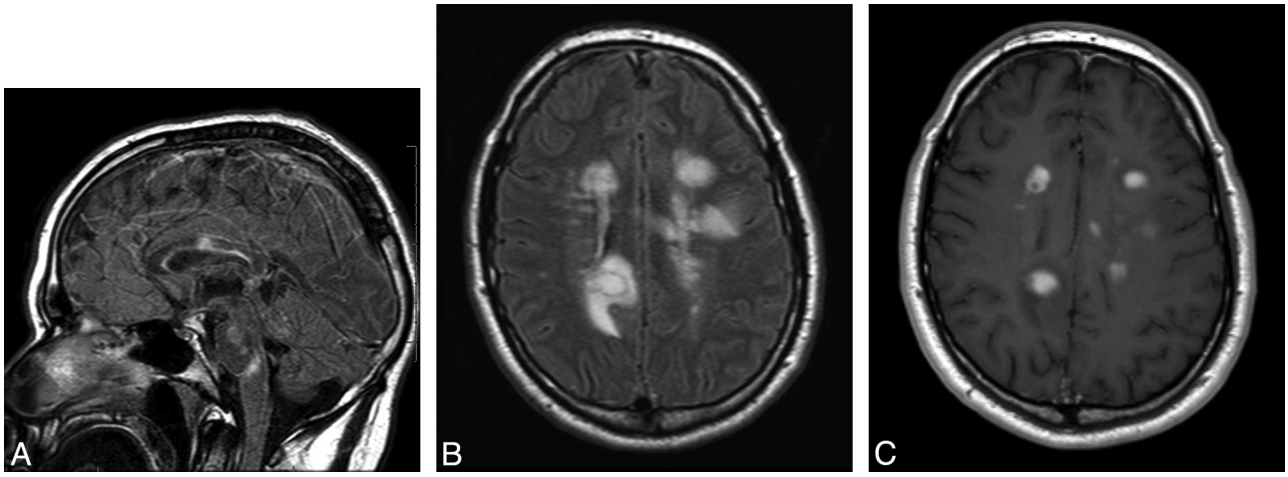

Fig 3. A 27-year-old man presented with numbness and weakness of both upper extremities and the left lower extremity, with multiple enhancing MR imaging lesions. He was prescribed high-dose β interferon (Rebif) soon after his initial clinical exacerbation but was switched to glatiramer acetate 1 year later due to breakthrough radiologic disease activity. The patient developed new right-sided paresthesias 3 years after his initial presentation. The MR imaging in this figure was performed when the new symptoms developed. *A*, FLAIR-weighted sagittal FSE image of the brain shows patchy high-signal-intensity areas involving the corpus callosum, brain stem structures, and cerebellum. *B*, FLAIR-weighted axial FSE image shows multiple patchy areas of high FLAIR signal intensity involving the corpus callosum and bilateral periventricular white matter with the presence of edema around a large right periatrial lesion. *C*, Postcontrast T1-weighted axial FSE image shows that a majority of the larger lesions exhibit intense patchy enhancement, suggestive of active demyelination.

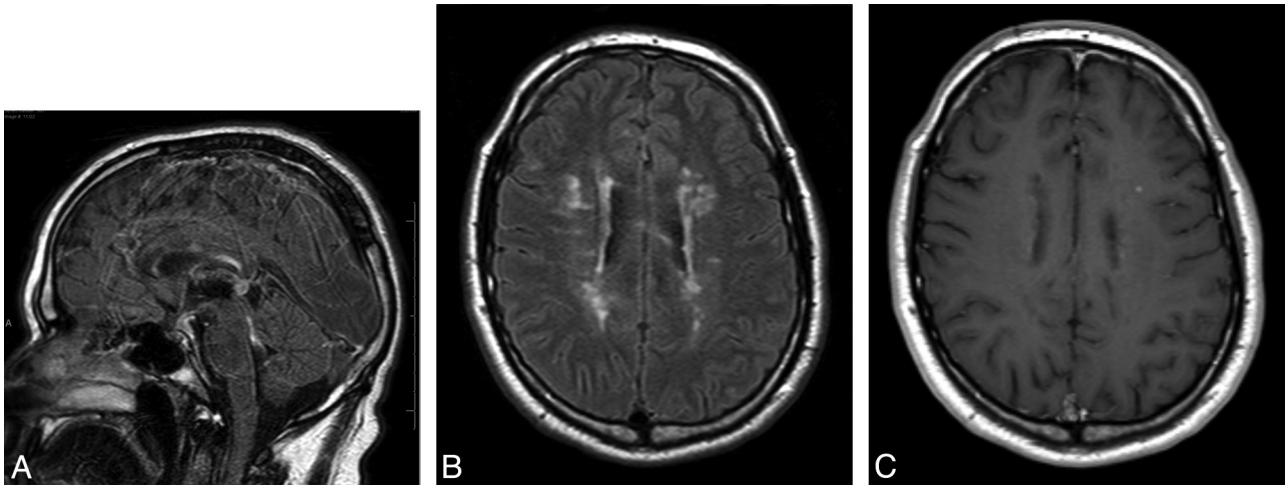

Fig 4. Within 1 month of the MR imaging shown in Fig 3, the patient was started on a course of natalizumab (Tysabri), 300 mg administered intravenously every 4 weeks. Repeat MR imaging after 6 months was performed. *A*, FLAIR-weighted sagittal FSE image of the brain shows improvement in the patchy high-signal-intensity area of the corpus callosum with resolution of lesions involving the brain stem structures and cerebellum. *B*, FLAIR-weighted axial FSE image shows marked improvement in the areas of demyelination involving the corpus callosum and bilateral periventricular white matter. *C*, Postcontrast T1-weighted axial FSE image shows only 1 small area of enhancement in the right periventricular white matter, with lack of enhancement of the rest of the enhancing lesions.

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