drug information perspectives

Volume 29 (4) 2010

Contents

NATALIZUMAB

TRADE NAME: Tysabri

CLASSIFICATION: Immunomodulator; multiple sclerosis treatment; disease-modifier; Selective Adhesion Molecule (SAM) inhibitor; alpha4-integrin antagonist; antiadhesion molecule

ACTION

Anti-inflammatory; inhibits the movement of leukocytes into areas of inflammation including the CNS. Inflammation in the brain is considered a major mechanism in multiple sclerosis (MS).

In MS, myelin sheath destruction and axonal loss may be due to inflammation caused by inflammatory cytokines produced by autoreactive T lymphocytes that penetrate the CNS. Natalizumab is a protein that contains 5% mouse-derived protein; a recombinant humanized IgG4 monoclonal antibody that selectively binds to alpha4-integrin, which is found on the surface of all white blood cells except neutrophils. The binding of natalizumab to alpha4-integrin inhibits the interaction between alpha4-integrin on leukocytes and Selective Adhesion Molecules on vascular endothelial cells. This interaction would normally help leukocytes cross from the endothelium into inflamed tissue; blocking it would reduce inflammation.

In inflammatory bowel disease, an increase in adhesion molecules facilitates the movement of leukocytes to the inflamed bowel, resulting in chronic inflammation. Natalizumab may block this inflammation.

PHARMACOKINETICS

Half-life: 11 days (however, effects last longer than predicted by the half-life; see Clinical Course)
Absorption: Maximum serum level attained after 3 hours.
Distribution: No data.
Metabolism: No data.
Elimination: Clearance is increased 30% with increased body weight and increased 3-fold if neutralizing antibodies are present.

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Special populations:

- ***Elderly***: No data.
- ***Adolescents***: Shorter half-life than in adults.
- ***Hepatic impairment***: No data.
- ***Renal impairment***: No data.
- ***Sex difference***: Does not influence pharmacokinetics.
- ***Race***: No data.
- ***Pharmacogenetics***: No data.

USES AND EFFICACY

Uses:
Effective symptomatic treatment of **Relapsing-Remitting Multiple Sclerosis**; only approved as monotherapy (single disease-modifying agent). The annualized relapse rate is reduced by 59% over 2 years. Benefit on sustained disease progression is less clear, although slightly fewer patients show worsened disability in the short-term. MRI results show a decrease in new or enlarging T2-hyperintense lesions and gadolinium-enhanced lesions.

Clinical course:
Lymphocyte levels remain elevated for about 12 weeks after discontinuation. Decreased CNS level of lymphocytes persists for 6 months after discontinuation. Clinical benefit in MS is detectable within the first year.

Major clinical trials

AFFIRM Study (2006): A randomized, double blind, placebo-controlled trial in 942 patients with relapsing remitting MS (average EDSS (disability) score 2.3) showed a relative decrease in the annualized relapse rate of 68% after one year and of 59% after 2 years. Progression of disability was reduced from 29% in the placebo group to 17% with natalizumab. On MRI, after two years there were 83% fewer new or enlarging hyperintense lesions and 92% fewer gadolinium-enhanced lesions with the study drug. Hypersensitivity reactions, headache during the infusion, and fatigue were the most common adverse effects. There were rare but numerically more cases of cancer and serious infection in the natalizumab group. [New Engl J Med 2006;354(9):899-910.] ***Study limitations***: Funded by the manufacturer.

SENTINEL study of combination therapy with interferon beta (Unapproved use in Canada)(2006): A randomized, double blind, placebo-controlled trial in 1196 patients with relapsing remitting MS (average EDSS 3.6-4.2) who were taking interferon beta-1a found an additional 55% relative reduction in the annualized relapse rate when natalizumab was added for two years. Annualized relapse rates for one and two years were 0.82 and 0.75 with interferon beta, and 0.38 and 0.34 with combination therapy, respectively. Progression of disability was lower with combination therapy (29% versus 23%, a 24% relative reduction and 6% absolute reduction). There were 89% fewer gadolinium-enhanced lesions with the combination. The study was stopped two months early because of two cases of progressive multifocal leukoencephalopathy (PML). [New Engl J Med 2006;354:911-923.] ***Study limitations***: Sponsored by the manufacturer. Although statistically significant, the difference in progression of disability is small in absolute terms (6%). Longer studies are needed to demonstrate reduced disability and the safety of this combination.

Comparisons
Vs. other therapies:
Although direct comparative trials have not been done, natalizumab appears to be as effective at reducing relapse rates as other available therapies for relapsing MS. The studies are difficult to compare due to different study designs; however, in the major trials the absolute difference in annualized relapse rates after two years of treatment was approximately 0.4-0.5 for natalizumab and 0.25 for glatiramer, suggesting greater benefit from natalizumab.

Advantages:

- Effective
- Treatment is just once a month

Disadvantages:

- Rare but life-threatening PML has occurred, for which there is no treatment, and symptoms of PML are difficult to distinguish from a relapse of MS.
- Given by IV infusion.
- Antibodies can develop that reduce efficacy and increase toxicity.

Place in therapy:
A second line therapy for maintenance treatment of relapsing-remitting multiple sclerosis, because of the risk of life-threatening PML. May be considered in patients who have not responded to or tolerated other therapies. The initial decision on the use of natalizumab is a difficult one, since it is the most effective drug for MS at this time, yet carries the risk of rare but frequently fatal PML, for which there is little information on effective treatment, risk factors, and monitoring. In Crohn`s disease there is less evidence to support its use, despite approval in the United States.

Investigational/Unapproved Uses:

- ***Combination therapy with natalizumab in Relapsing-Remitting MS***: The combination of glatiramer and natalizumab has reduced MRI activity but not clinical outcomes, and is not recommended due to the risk of progressive multifocal leukoencephalopathy with natalizumab.
- ***Crohn`s Disease (approved for restricted use in the United States):*** In inflammatory bowel disease, alpha4-integrin may be upregulated in lymphocytes in areas of GI inflammation. A subgroup of patients with moderate to severe Crohn`s disease may respond and achieve remission following a short induction course of three infusions. Responders are those with active inflammation as indicated by an elevated C-reactive protein level. Research has been hampered by high placebo responses in the clinical trials, making it more difficult to prove a benefit over placebo, and concern over possible PML (See SIDE EFFECTS).
- ***Ulcerative Colitis***: In inflammatory bowel disease, alpha4-integrin may be upregulated in lymphocytes in areas of GI inflammation. In an open study of 10 patients with active ulcerative colitis (Powell-Tucker colitis activity index greater than 4), a single IV dose of natalizumab was associated with a decrease in the activity index detectable one week later and remission in two patients. Further research is needed following this small, short study.

CONTRAINDICATIONS AND PRECAUTIONS

Contraindications:

- ***Hypersensitivity.***
- ***Existing or a history of progressive multifocal leukoencephalopathy (PML)*** (may cause PML).
- ***Immunomodulatory or immunosuppressive drugs*** (theoretically may increase the risk of PML. Corticosteroids may be used for short periods).
- ***Immune function impairment*** (since this drug alters immune function, increased infection risk and altered immune response is possible).

Precautions:

- ***Monitor for symptoms of progressive multifocal leukoencephalopathy (PML):*** Increased risk if immunosuppressed (AIDS, leukemia, lymphoma, organ transplantation); US guidelines specify patient evaluation after 3 months and then every 6 months thereafter; if PML is suspected, discontinue the drug immediately. Diagnosis may be confirmed with a gadolinium-enhanced MRI scan of the brain or CSF analysis for JC virus DNA. Note that tests for JC virus DNA have only 60-80% sensitivity, and MRI results may not be clearly distinguishable from MS lesions. Prediction of who will develop PML is difficult since JC virus infection is common in healthy people; however, some authorities recommend testing blood or urine for JC virus DNA since titres increase with prolonged therapy. There is no proven antiviral treatment, but removing any immunosuppression and restoring immune function by discontinuing the drug, and rapidly removing it by plasma exchange, has been partially successful. Patients who survive are left with neurologic sequelae due to irreversible demyelination. Early diagnosis and intervention are critical.
- ***Liver disease*** (can cause liver injury; assess at baseline and during therapy).

- ***Persistent antibodies to natalizumab*** (antibodies reduce drug levels and efficacy and increase risk of hypersensitivity reactions; if suspected because of poor response or adverse reactions, perform antibody testing after 3 months and repeat again to determine if transient; if persistent, stop treatment).
- ***Personal or family history of malignancy*** (controversial; some cases of malignancy reported).
- ***Children*** (no formal studies have been conducted).
- ***Report unexpected or serious reactions to Canada Vigilance***, Canada's adverse drug reaction monitoring program.

PREGNANCY AND LACTATION

Fetal changes were found following exposure at 2.3 times the human dose in pregnant monkeys (anemia, reduced platelet count). No teratogenic effects were found in monkeys exposed to 7 times the human dose. No human data in pregnancy; consider discontinuation.

No data on use in lactation. Consider discontinuation.

SIDE EFFECTS

Cardiovascular: Peripheral edema (5% vs. 1% with interferon beta alone). Pericarditis (1 case confirmed by rechallenge).

CNS: Fatigue (27% vs. 21% with placebo); headache (38% vs. 33% with placebo); anxiety (12% vs. 8% with interferon beta alone); suicidal ideation (0.6% vs. 0.3% with placebo); convulsions (case reports); post-lumbar puncture headaches (23%).

Dermatologic: See Hypersensitivity.

Hematologic: Increased blood lymphocyte levels by 70-80% (onset within 12 weeks, maximum at 24 weeks, reversible, may persist 16 weeks after discontinuation; mechanism: inhibition of their movement out of the vascular space). Decreased CNS level of lymphocytes (persists 6 months after discontinuation). Increased levels of monocytes, eosinophils and nucleated red blood cells (reversible). No change in neutrophil levels. Transient increase in hemoglobin levels. Decreased serum IgG levels.

Hepatic: Elevated liver enzymes, elevated serum bilirubin, liver injury (onset as early as day 6). Cholelithiasis (1% vs. 0.3% with placebo).

Hypersensitivity: Urticaria, dermatitis, anaphylactic or anaphylactoid reactions (4% of patients, 68% positive for natalizumab antibodies; may be immediate infusion-related reactions within 2 hours, or delayed).
- Post-infusion reactions (24% vs. 18% with placebo: headache, rash, urticaria, flushing, hypotension, hypertension, dizziness, chest pain, dyspnea, pruritus, fever, arthralgia, diaphoresis, tachycardia, neck pain; onset usually within 2 hours but may be delayed by hours or days; many patients are antibody positive; more common in early treatment or if treatment has been intermittent; stop infusion).
- Neutralizing antibodies (persistent in 6-13% of patients; onset within 12 weeks; associated with a decrease in serum levels and drug efficacy and an increase in the risk of hypersensitivity and infusion reactions).

Respiratory: Pharyngitis (7% versus 4% with interferon beta alone); sinus congestion (6% versus 3% with interferon beta alone).

Other: Progressive multifocal leukoencephalopathy (PML) (incidence estimated as 1 in 1000 patients treated for 18 months; risk increases with more infusions; a rare, usually fatal demyelinating infection caused by reactivation of JC virus in the CNS, usually seen in immunosuppressed patients; may occur in otherwise nonimmunosuppressed patients given natalizumab monotherapy; onset 8-37 months; symptoms: changes in neurological function will vary with the location of the lesions, but commonly include impaired mental function, weakness possibly on one side of the body, visual impairment, or myoclonus, similar to an MS relapse). Subclinical JC virus reactivation in urine and blood (increases over time; common).

- Infections (3.2% vs. 2.6% with placebo; may be serious; includes urinary tract infections, vaginitis, respiratory infections); serious herpes infections (cases).
- Cancer: Melanoma (3 cases). Primary CNS lymphoma (1 case). Ocular toxoplasmosis (1 case). In a controlled study, numerically more cases of cancer and serious infection occurred in the group receiving natalizumab than placebo.
- Multiple sclerosis relapses (case reports).
- Worsening of multiple sclerosis (a case).
- Falls (case reports).

INTERACTIONS

DRUG	EFFECT	MECHANISM	IMPORTANCE
Immunosuppressive drugs including antineoplastics and TNF-alpha inhibitors*	Risk of progressive multifocal leukoencephalopathy (PML) and infection	Unknown	Avoid; corticosteroids may be used for relapses but chronic corticosteroids should be slowly withdrawn; aminosalicylates may be used
Immunomodulator drugs including glatiramer, interferon beta*	Risk of progressive multifocal leukoencephalopathy (PML)	Unknown	Avoid; a washout period may be needed if switching therapy

* Immunosuppressants include 6-mercaptopurine, azathioprine, cyclosporine, and methotrexate. PML has also been reported in patients taking the following drugs: azathioprine, bevacizumab, corticosteroids, cyclophosphamide, etanercept, fludarabine, methotrexate, mycophenolate, rituximab.

PARENTERAL ADMINISTRATION
For intravenous infusion ONLY. Do not administer by IV push or IV bolus. Dilute only with 0.9% Sodium Chloride Injection. Withdraw 15 mL of natalizumab concentrate from the vial and inject this into 100 mL 0.9% Sodium Chloride Injection. Gently invert but do not shake. Infuse over 1 hour. Do not mix with other drugs.

DOSAGE

Adults:
- Multiple sclerosis: Intravenous: 300mg IV infusion once every four weeks.
- Crohn`s disease (not approved in Canada): Intravenous: 300mg IV infusion once every four weeks. Discontinue after 12 weeks if no response is detected.

Children:
No formal studies have been done. Anecdotally, children with multiple sclerosis ages 7 and 11 years have tolerated and possibly benefited from 300mg IV infusions once every four weeks.

Elderly:
- No data.

Hepatic impairment:
- No data.

Renal impairment:
- No data.

NURSING IMPLICATIONS
A hypersensitivity reaction may occur within 2 hours of the start of the infusion. Observe the patient during the infusion and for one hour afterwards for rash, fever, change in blood pressure, chest pain, or dyspnea. If these symptoms occur, stop the infusion and treat as needed.

This drug can cause a rare but life-threatening condition called progressive multifocal leukoencephalopathy (PML). Monitor for symptoms of this condition (weakness on one side of the body, change in gait, muscle spasms; vision changes, cognitive changes); discontinue treatment and advise the physician immediately if these occur.

Prolonged, regular therapy is required and a benefit in MS may not be detectable for months.

Store vials in the refrigerator. Do not freeze. Once diluted, the infusion solution should be used within 8 hours if kept refrigerated. Bring it to room temperature before infusing.

PATIENT INSTRUCTIONS
Natalizumab (na ta LIZ you mab) is used for the treatment of relapsing-remitting multiple sclerosis.

Before taking this medication, be sure to inform your physician if you are: immunosuppressed; pregnant or considering becoming pregnant; breastfeeding; or have a history of progressive multifocal leukoencephalopathy (PML); liver disease; infection including current infection, or allergic reactions to this drug. Tell your physician about all other medications that you are taking, including alternative health products and herbal products.

This medication is usually administered once every four weeks as an intravenous infusion.

In some people, a reaction can occur at the time of the infusion. Be sure to tell your nurse if you notice any unusual symptoms such as chest pain, difficulty breathing, chills, or itchy skin.

Rarely, this drug can cause a life-threatening condition called progressive multifocal leukoencephalopathy (PML). Monitor for symptoms of this condition (weakness on one side of the body, clumsiness, changes in vision, confusion). Discontinue this drug and advise your physician immediately if these symptoms or any other new neurological symptoms occur.

If you experience any other unusual effects while taking this drug, including unexpected nausea, lack of appetite, yellowing of the skin, or abdominal pain, inform your physician.

If you have experienced an unexpected or serious reaction to this drug, this can be reported to Health Canada?s monitoring program (tollfree telephone 1-866-234-2345, tollfree fax 1-866-678-6789). Note that this is not an emergency number.

PRESENTATION:
Injection: 300 mg/15 mL vial.

References are available on request.