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## Natalizumab (Tysabri®): New Hope for MS Patients

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### BACKGROUND

Multiple Sclerosis (MS) is an autoimmune inflammatory disease of the central nervous system marked by demyelination of the oligodendrocytes that leads to disability and eventual death.<sup>1</sup> Symptoms reflect the area of CNS involvement, and may include, but are not limited to, fatigue, vision problems, bowel or bladder dysfunction, changes in cognitive function, and balance or coordination problems. The course of the disease is highly variable, but it is generally marked by periods of stability or progression, alternating with periods of exacerbation known as relapses. About 400,000 persons in the United States are affected. MS often strikes between the ages of 20 and 50, and more commonly occurs in women than men.

Current treatment involves the use of immunomodulatory agents such as interferons or glatiramer acetate (Copaxone®) to slow the progression of the disease.<sup>2</sup> Treatment is symptomatic. Exacerbations are generally treated with short courses of high dose IV steroids ± prednisone taper.

Natalizumab, a recombinant humanized monoclonal antibody to alpha4-integrin, has an interesting regulatory history. It was originally approved under an accelerated priority review in November 2004 on the basis of one year of data from two clinical trials in patients with relapsing MS. The completed data (two years) from both trials were analyzed and published in 2006.<sup>3</sup>

### AFFIRM

A phase 3, blinded, placebo-controlled randomized controlled trial compared the rates of relapse and the rates of sustained progression of disability in 942 patients receiving natalizumab or placebo at 99 centers in Europe, North America, Australia, and New Zealand.<sup>4</sup> Patients between 18 and 50 with a diagnosis of relapsing multiple sclerosis who had had at least one relapse within the previous twelve months were randomized to receive either 300 mg natalizumab or placebo by IV infusion every four weeks. Natalizumab reduced the rate of progression by 42% over two years (HR, 0.58; 95% CI 0.43, 0.77, p<0.0001) and reduced the rate of relapse at one year by 68% (p<0.001) over placebo. Fatigue and allergic reactions were significantly more common in the natalizumab group. 1% of patients receiving natalizumab experienced anaphylactic reactions, and 6% developed persistent antibodies to the drug.

### SENTINEL

A phase 3, blinded placebo-controlled randomized controlled trial compared the rates of relapse and the cumulative probability of progression in 1171 patients taking interferon beta-1a with either natalizumab or placebo at 124 centers in Europe and the United States.<sup>5</sup> Patients between 18 and 55 with a diagnosis of relapsing-remitting MS who had received interferon beta-1a for at least twelve months and had had at least one relapse during the previous twelve months received either 300 mg natalizu-

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mab or placebo by, IV infusion every four weeks in addition to interferon beta-1a 30 micrograms IM once weekly. Combination therapy reduced the rate of progression by 24% (HR, 0.76, 95% CI 0.61, 0.96,  $p=0.02$ ) and reduced the annualized rate of relapse at two years by 41% (0.74 vs. 0.34,  $p<0.0001$ ). Anxiety, pharyngitis, sinus congestion, and peripheral edema were significantly more common in the combination therapy groups. 1.9% of patients receiving interferon and natalizumab had a hypersensitivity reaction (non-anaphylactic). 6% of patients receiving combination therapy developed persistent antinatalizumab antibodies, with an associated increase in infusion-related events and decrease in efficacy.

Four months after approval, sales of natalizumab were suspended to investigate two case reports of progressive multifocal leukoencephalopathy (PML) in MS patients receiving the drug. PML is an opportunistic viral infection that usually results in severe disability or death. A third case of PML developed in a patient with Crohn's disease receiving Tysabri® in a separate clinical trial. Two of the three patients died. An extensive review of the clinical trial safety data showed no further cases of PML in the trial subjects, and marketing was resumed under a restricted distribution program in July 2006.<sup>3</sup>

Under the TOUCH (Tysabri® Outreach: Unified Commitment to Health) program, prescribers, infusion centers, and pharmacies must be registered in order to prescribe, distribute, or infuse the drug. Tysabri® may only be given to patients who are enrolled in and meet the criteria of the program.<sup>6</sup>

## MECHANISM OF ACTION

The neurologic damage that occurs in MS is thought to be mediated by inflammatory leukocytes, specifically T lymphocytes that enter the CNS and attack the myelin.<sup>3</sup> Integrin is a protein that is expressed on all leukocytes (except neutrophils) and is responsible for the adhesion of leukocytes to the endothelium that is necessary for movement of these cells from the peripheral blood into cerebral tissue. Tysabri® prevents the binding of T lymphocytes to the endothelium, and thus, their movement across the blood-brain barrier, which prevents further neurologic damage.

## PREPARATION AND INFUSION

Tysabri® is supplied in 15 mL vials of preservative-free concentrate containing 300 mg natalizumab.<sup>7</sup> It is diluted in 100 mL of 0.9% normal saline and given as a continuous infusion over one hour once monthly. If not administered immediately after preparation, it can be refrigerated and used within 8 hours. Tysabri® should not be given IV push or by bolus injection. Dosing adjustments are not currently recommended for renal or hepatic impairment.

## PRECAUTIONS AND CONTRINDICATIONS

Tysabri® is rated Category C. It is not known whether or not it is excreted in breast milk. Safety and efficacy has not been established in pediatric populations. Safety of doses over 300 mg has not been evaluated. Tysabri® is not recommended in patients who are immunocompromised or who are currently taking anti-neoplastics, immunosuppressants, or immunomodulators. A washout period is required before initiating natalizumab in patients receiving treatment with other immunomodulators or immunosuppressants, and may range from 6 weeks to more than 6 months depending on the treatment being used.<sup>8</sup> It is contraindicated in patients with current or previous PML. The most common infusion-related (within 2 hours of start of infusion) reaction is headache and is treated symptomatically. The incidence of immediate hypersensitivity reactions is approximately 1%.

## CONCLUSIONS

Tysabri® is a promising new drug for relapsing forms of multiple sclerosis. Although no head-to-head trials have been done, its efficacy appears equal to and may surpass the other currently available disease-modifying therapies. Further clinical trials are needed. It also shows promise in the treatment of moderate to severe Crohn's disease and the joint advisory committees of the FDA have recently recommended its approval for this indication.<sup>9</sup>

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## Intraosseous Infusion- What is it?

Cathie Jamieson, BS Pharm

### HISTORY

Intraosseous (IO) infusion is a method of administering medications, fluids, blood products, etc. via injection directly into the soft bone marrow interior. Drinker, Drinker, and Lund<sup>1</sup> first suggested intraosseous infusion as an alternative route of administration with the first therapeutic use of IO access being reported in 1934.<sup>2</sup> IO infusion was popular in the 1930s and 1940s<sup>3</sup> but with the advent of the intravenous catheter, this administration route fell out of use.

The American Heart Association (AHA)<sup>4</sup> included intraosseous infusion as an option for delivery of resuscitation drugs. Drugs administered during cardiac arrest have historically been done via the intravenous route (IV) or the endotracheal (ET) route. Due to the poor absorption of medications administered by the ET route, as well as the optimal dose of the medication being unknown, the ET route of administration is to be reserved for those patients who do not have IV or IO access.

Circulation of agents administered via IO infusion is thought to occur via the medullary cavity of the bone. The time from injection via IO infusion to entry of the substance into the systemic circulation is thought to be equivalent to that of the IV route.

### INDICATIONS OF USE

Intraosseous infusion is a quick way to establish access for the rapid infusion of substances in emergency situations and resuscitation efforts. It is a temporary emergency measure that is indicated in life-threatening situations where IV access fails. Failure to achieve IV access is defined by 3 attempts at IV access or the accessing of an IV site has taken greater than 90 seconds.<sup>5</sup>

Other indications of use include burns, obesity, and edema where establishing IV access is difficult. In situations where rapid high-volume fluid infusion is necessary, such as hypovolemic shock and burns, the IO route of administration is an option.

IO access is available for administration of local anesthesia if access is needed to the systemic venous circulation.<sup>6</sup> Buck, et al.,<sup>3</sup> indicate that IO access may be used to obtain mixed-

venous blood samples for blood chemistry, blood gases, and type and cross studies.

### CONTRAINDICATIONS OF USE

IO access is contraindicated in certain situations.<sup>2</sup> **Ipsilateral fracture of the extremity** and **previous attempt or placement in the same leg or site** may result in extravasation and an increased risk of compartment syndrome.

In patients with bone disorders, such as **osteogenesis imperfecta (Brittle Bone Disease)**, **Osteopetrosis (Marble Bone disease and Albers-Schonberg disease)**, and **osteoporosis**, IO access is contraindicated due to the increased risk of causing a bone fracture.

**Infection at entry site** is also considered a contraindication to use of IO access due to the increased risk of seeding the infection.

### COMPLICATIONS

Complications are rare with the proper placement of the IO access needle.

Eslami<sup>2</sup> states that the local infection rate is less than 3%. Cellulitis and osteomyelitis result due to poor antiseptic technique or prolonged needle placement (over 72 hrs).<sup>6</sup>

Poor technique and prolonged infusion of blood or fluids may result in extravasation into the surrounding soft tissue.

Compartment syndrome is an acute medical problem following injury or surgery, and may occur after IO placement. In this syndrome, there is an increase in pressure (usually caused by inflammation) within a confined space. This inflammation impairs blood supply, which may result in nerve damage and muscle death without prompt treatment.

Bone fractures may occur from excessive force. The use of excessive force may also result in a through-to-through penetration of the IO needle.

Pneumothorax, mediastinitis, or surrounding organ and tissue injury may result after sternal IO punctures.

### DRUG ADMINISTRATION

There are some considerations to the administration of medications via the IO route.<sup>3</sup> Currently, there are no resuscitation drugs that are considered contraindicated for IO administra-

tion. Infusion pumps are also recommended when administering continuous infusions via the IO route.

The standard dosing for drugs administered via the IO route is that same as for the IV route of administration. Some drugs may exhibit a depot effect, where the drug will remain in the medullary cavity, resulting in a lower peak serum concentration and a slower time to reach peak concentration levels. This effect has been seen mostly with ceftriaxone, chloramphenicol, phenytoin, tobramycin, and vancomycin. Pollack, et al.,<sup>7</sup> suggest that a higher dose of ceftriaxone may be more appropriate for IO administration. To minimize the depot effect, it is recommended flushing the line with 3 to 10 mL of NaCl 0.9% after each drug administration.

## CONCLUSION

IO access can be established in all age groups and can be a valuable tool, especially in a resuscitation effort. Access often can be achieved in 30 to 60 seconds. AHA<sup>4</sup> states that the IO route of administration is preferred over the ET route and that any drug or fluid that is administered IV can be given IO.

Proper antiseptic technique needs to be used during placement of the IO apparatus. With proper technique and placement, the rate of complications is low.

The removal of the IO access should be done as quickly as possible to decrease the potential for infection. This is accomplished by establishing viable IV access as quickly as possible.

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## Cathie Jamieson's Bio

Cathie Jamieson, the new clinical coordinator/residency director in pharmacy joined the Highline Medical Center healthcare team in June.

Originally born in Illinois, she has lived in many areas of the country due to her father being a civil servant for the government. She has lived in Maryland, Utah, and California. Her most formative years were spent in West Virginia, where she graduated from high school. After high school graduation, Cathie and her family moved to Washington State in 1976.

Cathie attended Western Washington College (now Western Washington University) for the first two years of her college life. After that, she attended the University of Washington, where she graduated with dual degrees, a BS Pharmacy and a BA Psychology.

Upon graduation from college, Cathie went to work at West Seattle Community Hospital. After the birth of her daughter, the work place changed to St. Francis Hospital in Federal Way, where Cathie stayed for the next 17 years.

Being the Internal Medicine Pharmacist Specialist, Cathie was involved in many projects. A couple of key initiatives that she is especially proud of are the development and implementation of the pharmaceutical care and a clinical decision making programs for pharmacists.

The best aspect of any job for Cathie is the ability to teach and mentor. While at St. Francis, Cathie was responsible for being the main preceptor for students/interns/residents. She provided educational offerings to nursing staff, as well as to pharmacy staff, on a variety of subjects.

On a personal note, while Cathie did graduate from the U of WA, she does not say it too loudly as she is involved in a mixed marriage. Yes indeed, she is married to a Washington State Cougar !!! She lives with her husband Scott, three out of five children (the two 19 year olds are off trying to be grown ups), two cats, one dog, one goat, and four chickens on 2 acres in Maple Valley. In her spare time, she loves to travel (mostly to follow Cougar football or see her daughter play softball in college), tend her garden (much to her husband's dismay because it usually involves some sort of excavation on his part), read, fish, and go to the beach.

When you see her, please welcome Cathie to the Highline Medical Center family !!!

## Pharmacy Residency Education and Training

Miller, WA. Changing the structure of pharmaceutical education to require doctor of pharmacy and postgraduate residency education and training. *Pharmacotherapy* 2006;26(5):587-593.

Abstracted by: David T. Tsung, Pharm.D.

The postgraduate pharmacy education has evolved from an on-the-job training in the 1930s to a nationally recognized residency system today. In 1965, ASHP released the first pharmacy residency accreditation standard. Since then pharmacy residency programs have been developed quickly around the country. Between 1996 and 2005, the number of pharmacy residency programs has grown even more rapidly. The number of accredited residency programs grew from 391 to 761 and the number of residents increased from approximately 700 to 1400 per year – nearly 100% growth in both areas. Despite this impressive growth, these numbers merely represent 15 to 20% of pharmacy graduates completing a residency prior to entering pharmacy practice.

Pharmacy residency programs should be a part of the continuum of pharmaceutical education. JCPP envisions that all pharmacy graduates should be able to “have the authority and autonomy to manage medication therapy and will be accountable for patients’ therapeutic outcomes.” In other words, pharmacy graduates should be able to function independently as pharmacotherapy experts upon graduation. JCPP’s vision is contrary to the idea of providing “pharmacy graduates with fundamental problem-solving skills necessary for practice” and relies on work experience to develop advanced pharmaceutical knowledge over time.

As the pharmacists’ duties become more complex, require more specialized knowledge and ability, it is evident that a pharmacy residency should be a prerequisite to enter practice. However, residency programs should not be used to make up for the deficiencies from the classrooms. Instead, residency programs should build on the knowledge and skills acquired in the classrooms. Pharmacy residencies are to provide the new practitioners the opportunity to mature clinical skills, build self-confidence, and sharpen problem-solving skills.

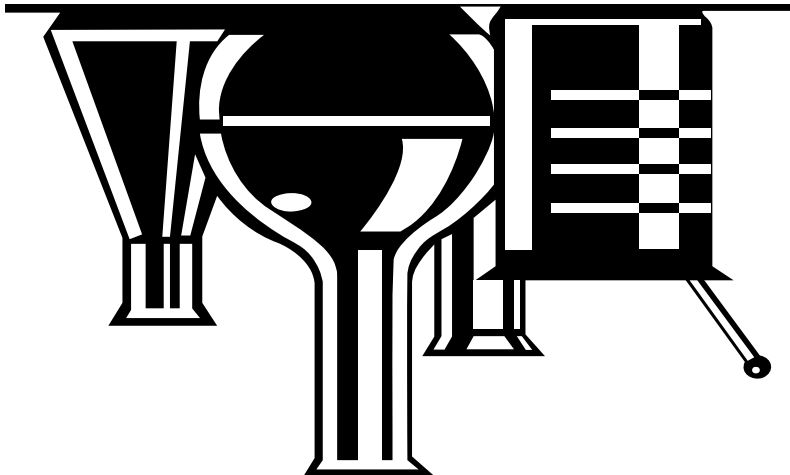
In order to provide pharmacy graduates with the number of qualified residencies needed, currently accredited residency programs are encouraged to take on more residents. For each qualified preceptor in a given residency program, the program should take one resident. Assuming each residency program has ten preceptors this will yield approximately 4355 PGY1 and 840 PGY2 resident positions, enough to offer 50% of annual pharmacy graduates.

The pharmacy education and the profession of pharmacy itself are undergoing drastic restructuring. The new education outcomes requirements set forth by ACPE force schools of pharmacy around the country to reevaluate and reorganize their curriculum. Various pharmacy practice settings require more advanced and sophisticated pharmaceutical skills. These changes drive up the prerequisite of entry-level pharmacists. Since this article was published, ASHP passed a resolution in the summer of 2007 calling for the completion of a pharmacy residency, as a prerequisite for all pharmacists who engage in direct patient care, by 2020. ASHP officials noted that this resolution would strengthen the bid for funding for PGY2 residencies from CMS.

Highline Medical Center is a fully accredited ASHP pharmacy resident-training site with nine preceptors on-board. Highline offers two pharmacy practice resident positions annually. The areas of training include, but not limited to: general medicine, critical care, geriatric psychiatry, ambulatory anticoagulation, hematology/oncology, staffing skills, and administration. Residents will also have the opportunity to complete one or two elective rotations.

### Abbreviations

ASHP – American Society of Health-System Pharmacists; formally known as American Society of Hospital Pharmacists  
JCPP – Joint Commission of Pharmacy Practitioners  
PGY1 – postgraduate 1-year; pharmacy practice residency  
PGY2 – postgraduate 2-year; specialty residency  
ACPE – Accrediting Council for Pharmacy Education  
CMS – Center for Medicare and Medicaid Services



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