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Natalizumab in pediatric multiple sclerosis patients

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***Abstract*:** Pediatric multiple sclerosis (MS) comprises 2–5% of all cases of MS. Although first-line disease-modifying therapy (DMT) including interferons and glatiramer acetate appear to be well tolerated in this population, recent work has suggested that a growing number of children suffer from disease which is resistant to treatment with these therapies. Natalizumab is a therapy which, although associated with a 1 : 1000 risk for progressive multifocal leukoencephalopathy (PML), has been shown to be well tolerated in the adult population and may lead to disease remission in adults with highly active disease. Reports of use of this therapy in the pediatric population with highly active disease have been published. This paper reviews current experience with the use of natalizumab in the pediatric MS population, with attention to potential risks and possible long-term outcomes in this population.

***Keywords*:** adolescent, breakthrough disease, multiple sclerosis, natalizumab, pediatric, therapy, treatment

Background and introduction

Pediatric multiple sclerosis (MS) comprises 2–5% of all cases of MS. A growing body of data has suggested that US Food and Drug Administration (FDA)-approved medications used for the treatment of MS in adults, often referred as first-line disease modifying therapy (FL-DMT), including the interferons (IFNs) and glatiramer acetate (GA), are relatively well tolerated in the pediatric population [Ghezzi *et al.* 2009, 2005; Mikaeloff *et al.* 2008, 2001; Pohl *et al.* 2007, 2005; Banwell *et al.* 2006; Kornek *et al.* 2003].

However, the efficacy of these agents is often limited and may only result in a 30% reduction in relapse rate in adults. Similarly, recent data have shown that many children with MS who are treated with FL-DMT do not tolerate or achieve adequate disease control on these therapies. Indeed, in a large retrospective study of children in the US, approximately 1/5 of children on IFN and GA discontinued these therapies due to poor tolerance or compliance, and over 1/4 changed therapies due to breakthrough disease [Yeh *et al.* 2009]. In children with breakthrough disease, chemotherapy and other newer agents including natalizumab, mitoxantrone, mycophenolate mofetil, rituximab and daclizumab, and cyclophosphamide, in addition to pulse steroids/intravenous immunoglobulin (IVIG)/combination therapies with FL-DMT have been used with good results [Yeh *et al.* 2009; Makhani *et al.* 2009]. This paper reviews current experience with the use of natalizumab in the pediatric MS population, with particular attention paid to the potential risks and possible long-term outcomes in this population.

Natalizumab: mechanism of action

Natalizumab, a recombinant, humanized monoclonal antibody, binds to the α4 subunit of α4β1 (very late antigen-4 [VLA-4]) and α4 β7 integrins (adhesion molecules), hindering the interaction between VLA-4 and its counter-receptor, vascular endothelial adhesion molecule-1 (VCAM-1). Disruption of these molecular interactions antagonizes the leukocyte–endothelium adhesion processes necessary for efficient migration of leukocytes across the blood–brain barrier endothelium, reducing the recruitment of immune cells into sites of inflammation within the central nervous system (CNS) [Archelos *et al.* 1999]. This has been confirmed in animal models using acute experimental autoimmune encephalomyelitis (EAE) [Coisne *et al.* 2009; Yednock *et al.* 1992].

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Safety and efficacy

Two pivotal, randomized, placebo-controlled phase III clinical trials showed that natalizumab was effective for the treatment of relapsing–remitting (RR) MS in adults (defined as individuals with RRMS between the age of 18 and 50) [Polman *et al.* 2006; Rudick *et al.* 2006]. In the AFFIRM trial [Polman *et al.* 2006], natalizumab treatment (300 mg, IV infusion, once every 4 weeks) was compared with placebo. In the SENTINEL trial, the combination of natalizumab plus IFN-β-1a (natalizumab: 300 mg, intravenous infusion, once every 4 weeks; IFN-β-1a 30 μg, intramuscular injection, once weekly) was compared with placebo plus IFN-β-1a [Rudick *et al.* 2006]. Both trials demonstrated the efficacy of natalizumab treatment in reducing relapse rate, visual loss, disease progression and occurrence of new magnetic resonance imaging (MRI) lesions in MS [Radue *et al.* 2010; Havrdova *et al.* 2009; Balcer *et al.* 2007; Miller *et al.* 2007].

Natalizumab appears to be effective for adults with highly active RRMS. Subgroup analysis of patients with highly active RRMS in the AFFIRM and SENTINEL trials showed a reduction in disability progression of 64%, and a reduction in relapse rate by 81% in treatment naïve patients with highly active disease and 58% and 76% in patients with highly active disease despite treatment with IFN-β-1a [Hutchinson *et al.* 2009]. This finding has been reproduced in multicenter studies involving German-speaking and Danish populations [Putzki *et al.* 2010; Oturai *et al.* 2009].

A large proportion of adults with RRMS may be able to experience significant improvement in relapse rate on natalizumab: *post hoc* analysis of the AFFIRM data has shown that almost 2/3 (64%) of patients treated with natalizumab *versus* 39% of those on placebo were free of clinical disease activity. Fifty-eight percent *versus* 14% were free of radiological disease activity and 37% *versus* 7% were free of combined activity over 2 years [Havrdova *et al.* 2009]. Conflicting evidence regarding rebound phenomena after discontinuation of natalizumab exists. Increased T2 lesion burden has been noted in a small study ($n = 21$) of patients after natalizumab cessation. Patients in this study were participants in the SENTINEL and AFFRIM trial. They were divided into two groups: one receiving placebo in the blinded portion of the study then switched to natalizumab in the open-label section of the study, and another receiving natalizumab while blinded then kept on natalizumab in the open-label section. Importantly, those patients who were more likely to develop increased T2 lesion burden after natalizumab cessation were on therapy for a shorter period of time and fell into the placebo-natalizumab group [Vellinga *et al.* 2008]. The significance of these findings is unclear.

By contrast, a small 14-month follow-up study of patients ($n = 23$) who discontinued natalizumab showed that decreased lymphocyte cell numbers and altered cell ratios returned to normal, and that the majority of patients were clinically stable after cessation of the therapy for the follow up period [Stüve *et al.* 2009]. Importantly, most of the patients in this study were treated with other immunomodulatory medications, primarily IFNs, after cessation of natalizumab. Thus, it is not clear whether the patients' clinical stability can be attributed to natalizumab or the immunomodulatory therapy initiated after natalizumab cessation.

In general, natalizumab is reported to be well tolerated in the adult population. Adverse events that were significantly more common in adults taking natalizumab compared with placebo in the AFFIRM trial were fatigue and allergic reactions. Infusion reactions, described as events occurring within two hours after the start of the infusion, were only slightly higher in natalizumab (24%) *versus* placebo (18%) ($p = 0.04$) treated patients in the AFFIRM trial [Polman *et al.* 2006]. Recently, the FDA reported six individuals with clinically significant elevations in serum transaminases and bilirubin, four of which occurred after the first infusion, suggesting the need to monitor liver function tests in individuals being treated with natalizumab [Bezabeh *et al.* 2010].

Pediatric use of natalizumab

Large, controlled studies of the safety and efficacy of natalizumab have not been performed in the pediatric MS population. Two published manuscripts have described the use of natalizumab in a total of four children who had highly active disease or poor tolerance of first-line therapies [Borriello *et al.* 2009; Huppke *et al.* 2008]. The first, a case report, described a 12-year-old girl experiencing clinical relapses and ongoing disease activity on MRI

(gadolinium-enhanced lesions) despite treatment with IFN for 10.5 months. Treatment with natalizumab 300 mg/day resulted in cessation of MRI and clinical evidence of disease activity for the 11-month follow-up period described [Borriello *et al.* 2009].

In the second case series, dosing was 3–5 mg/kg/dose/month IV. Again, relapses persisted despite treatment with IFN and GA in all children prior to introduction of natalizumab. Use of natalizumab resulted in the cessation of MRI and clinical relapses in all three children after follow up for 15, 16, and 24 months. The medication was well tolerated by these children [Huppke *et al.* 2008].

Our group recently described 24 pediatric MS patients treated with natalizumab as part of the US Network of Pediatric MS Centers. All children received a dose of natalizumab 300 mg/month, following the standard adult treatment protocol. Most of the patients were adolescents, with an average age at time of treatment initiation of 14 years (SD ± 2.3 years) [Yeh *et al.* 2010]. The majority of these children (75%) received the therapy as a fourth or fifth agent, suggesting that most children receiving this therapy had failed multiple FL-DMTs [Yeh *et al.* 2009]. The medication was relatively well tolerated. Twenty patients (83%) had a very good response, remaining stable with respect to MRI and clinical parameters for the extent of the follow-up period (average 1.5 years) [Yeh *et al.* 2010]. However, four patients discontinued therapy due to poor tolerance and/or hypersensitivity reaction.

Dosing in the pediatric population has not been established, as can be seen from the varying approaches in the published literature (3–5 mg/kg/dose *versus* 300 mg/dose). It is possible that doses as low as 3 mg/kg/dose may be effective: a study of its use in Crohn's disease in the pediatric population suggested a mean alpha-4 integrin receptor saturation of 93% at 2 hours and <40% at 4 weeks after the first and third infusions at a dose of 3 mg/kg/dose [Hyams *et al.* 2007].

Antinatalizumab antibodies, efficacy and hypersensitivity reactions

Antinatalizumab antibodies appear to have an influence on medication efficacy. These antibodies were seen transiently in 3% and persistently in 6% of the SENTINEL and AFFIRM patients [Calabresi *et al.* 2007]. Patients with persistently positive antinatalizumab antibody titers have been shown to experience increased disability progression, relapse rate, and MRI lesion formation compared with antibody negative patients [Calabresi *et al.* 2007; Polman *et al.* 2006]. One child in the US series discontinued therapy due to a hypersensitivity reaction associated with antibodies to natalizumab [Yeh *et al.* 2010]. Hypersensitivity reactions, described as hypersensitivity, allergic reaction, analyalytic/anaphylactoid reaction, urticaria, allergic dermatitis, or hives, were reported in 4% of patients enrolled in the AFFIRM trial frequently associated with the presence of antinatalizumab antibodies [Polman *et al.* 2006].

A delayed (2–3 days after treatment) serum-sickness type reaction (type III) has also been described in adult patients, and may be associated with antinatalizumab antibodies [Hellwig *et al.* 2008; Krumbholz *et al.* 2007]. One study suggests the incidence of this type of reaction may be as high as 10% (4/40 patients) [Hellwig *et al.* 2008]. This type of reaction may be treated with the use of steroids and reduction of the infusion rate, although discontinuation of natalizumab should take place with antibody-positive patients [Hellwig *et al.* 2008; Krumbholz *et al.* 2007]. This type of hypersensitivity reaction has not been described in the pediatric population yet.

Progressive multifocal leukoencephalopathy and other significant adverse effects

Progressive multifocal leukoencephalopathy

Important long-term risks have been described in relation to the use of natalizumab in the adult population with MS. The first three reports of cases of progressive multifocal leukoencephalopathy (PML) in relation to treatment with natalizumab were published in 2005 [Kleinschmidt-DeMasters and Tyler, 2005; Langer-Gould *et al.* 2005; VanAssche *et al.* 2005]. PML is a rare, often fatal central nervous system infection caused by the JC polyomavirus. These reports prompted its withdrawal from the US market by the FDA that year. After extensive review, including evaluation of over 3000 patients who had been treated with the drug, the risk of development of PML was found to be 1 : 1000 [Yousry *et al.* 2006].

Owing to the associated risk of PML, an individualized risk/benefit assessment is necessary prior

to initiation of therapy, and a high level of clinical vigilance must be maintained during the therapy. In March 2006, the Peripheral and Central Nervous Systems Drugs Advisory Committee of the FDA approved making natalizumab available under a surveillance plan (TOUCH program). This program includes the following features: (1) the drug can only be prescribed, distributed and infused by prescribers, infusion centers, and pharmacies registered with the program; (2) natalizumab can be administered only to patients enrolled in the program; (3) MRI scans must be done prior to initiation of the therapy; (4) patients on natalizumab must be evaluated at 3 and 6 months after the first infusion and every 6 months thereafter, with regular reports to the manufacturer (Biogen Idec).

Initial reports of PML associated with natalizumab suggested that patients on a concomitant therapy could be at higher risk of developing this complication. However, as experience with the drug has grown, it has become clear that this risk is not limited to these individuals. In 2009, a case report of an individual patient on natalizumab monotherapy who developed PML was published [Linda *et al.* 2009], and by late 2009, a total of 28 cases had been confirmed, some of which were associated with monotherapy. Eight of these cases were fatal [Clifford *et al.* 2010]. It is now clear that risk increases with length of treatment: average time on therapy in these patients was 25 months (range 6–80 months) [Clifford *et al.* 2010].

Treatment for PML in natalizumab-associated cases includes the use of plasma exchange and immunoadsorption to eliminate the presence of the drug and restore immune effector function [Khatri *et al.* 2009]. Unfortunately, this is often followed by immune reconstitution inflammatory syndrome (IRIS), which leads to widespread CNS inflammation, often treated with pulse steroids [Clifford *et al.* 2010; Wenning *et al.* 2009]. At this point, screening of urine or serum for JC virus does not appear to be helpful in the early detection of PML in natalizumab-treated patients or risk stratification of these patients, as subclinical reactivation in JC virus may occur frequently in patients on natalizumab [Chen *et al.* 2009].

There have been no cases of natalizumab-related PML reported in the pediatric population with MS. Importantly, studies have shown that fewer than 25% of immunocompetent children have been infected with JC virus as opposed to half or two thirds of adults. The number increases with age: fewer than 15% of children under the age of 10 have been infected with JC virus [Polo *et al.* 2004; Knowles *et al.* 2003]. As PML is the result of reactivation of a primary, usually asymptomatic infection with the JC virus, children may be at lower risk for this condition, as long as JC virus infection has not yet occurred. Epidemiologic studies suggest this may be true: only one of 79 consecutive confirmed cases of PML in a Norwegian county was under the age of 10 [Stoner *et al.* 1988].

Few reports of PML in the pediatric population exist; it has been described in relation to primary immunodeficiency syndromes, such as Wiskott–Aldrich syndrome [Katz *et al.* 1994] and hyperimmunoglobulin E recurrent infection syndrome [Angelini *et al.* 2001] as well as in acquired immunodeficiency syndromes, such as in HIV-infected children [Liptai *et al.* 2007; Nuttall *et al.* 2004; Singer *et al.* 1993; Berger *et al.* 1992]. In most of these cases, the children were 12 years of age or older, although it has also been described in 5-, 10-, and 11-year-old children with HIV and inherited immunodeficiency syndromes [Katz *et al.* 1994; Berger *et al.* 1992]. Taken together, this literature suggests that PML does occur in the pediatric population, but possibly at lower rates than in the adult population. Whether children on immunosuppressive therapies truly have lower risk of developing PML, however, remains to be seen in future studies.

Other serious outcomes

Although the AFFIRM trial reported a similar incidence of cancer in the control and treatment groups (1 *versus* 5 patients, <1% in both groups) [Polman *et al.* 2006], more recently, reports of melanoma and primary CNS lymphoma have been described in relation to natalizumab [Schweikert *et al.* 2009]. Longitudinal studies are needed to clarify the association of these diseases with natalizumab use.

There have been no reports of cancer in pediatric patients treated with natalizumab. The rate of primary central nervous system lymphoma is 0.02/100,000 in childhood, with a 15-fold increase in risk in the 30 s, to a 100-fold increase in risk in the 70 s [Schweikert *et al.* 2009]. It is unknown how immunosuppression changes this risk.

However, as immunosuppression may be a predisposing condition leading to the development of primary CNS lymphoma, vigilance in the pediatric population receiving natalizumab is necessary.

Conclusion

Natalizumab appears to be well tolerated in the pediatric MS population. Its use thus far has been limited to children with highly active MS who have experienced breakthrough disease despite the use of FL-DMTs. Dosing of natalizumab in the pediatric population has not been established yet. It appears to reduce relapse rate in case series with limited follow up. The optimal duration of treatment with natalizumab in this population has not been established; the risks and benefits of prolonged treatment must be weighed given the known increased risk of development of PML in the adult population which is associated with longer duration of therapy. Use of natalizumab in this population should be approached with caution as development of serious side effects reported in the adult population, including PML and cancer may be anticipated as experience with the medication in pediatric MS patients grows.

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Conflict of interest statement

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