

Neurology[®]

Safety and efficacy of natalizumab in children with multiple sclerosis

A. Ghezzi, C. Pozzilli, L.M.E. Grimaldi, et al.

Neurology 2010;75;912

DOI 10.1212/WNL.0b013e3181f11daf

This information is current as of May 2, 2012

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://www.neurology.org/content/75/10/912.full.html>

Neurology® is the official journal of the American Academy of Neurology. Published continuously since 1951, it is now a weekly with 48 issues per year. Copyright © 2010 by AAN Enterprises, Inc. All rights reserved. Print ISSN: 0028-3878. Online ISSN: 1526-632X.



Safety and efficacy of natalizumab in children with multiple sclerosis



A. Ghezzi, MD
C. Pozzilli, MD
L.M.E. Grimaldi, MD
V. Brescia Morra, MD
F. Bortolon, MD
R. Capra, MD
M. Filippi, MD
L. Moiola, MD
M.A. Rocca, MD
M. Rottoli, MD
P. Sarchielli, MD
M. Zaffaroni, MD
G. Comi, MD

Address correspondence and reprint requests to Dr. Angelo Ghezzi, Centro Studi Sclerosi Multipla, Via Pastori 4, Ospedale di Gallarate, 21013 Gallarate, Italy
angelo.ghezzi@aogallarate.it

ABSTRACT

Objective: To describe the effect of natalizumab in the treatment of subjects with active multiple sclerosis (MS) treated before the age of 18 years.

Methods: Nineteen pediatric subjects with MS (mean age 14.6 ± 2.2 years, mean number of attacks 5.2 ± 1.9 during the pretreatment phase of 27.7 ± 19.7 months, median pretreatment Expanded Disability Status Scale score [EDSS] 2.5, range 1.0–5.0) were treated with natalizumab at the dose of 300 mg every 28 days. After treatment initiation, patients were reassessed clinically every month; brain MRI was performed at baseline and every 6 months.

Results: Patients received a median number of 15 infusions (range 6–26). A transient reversible worsening of preexisting symptoms occurred in 1 subject during and following the first infusion. All the patients remained relapse-free during the whole follow-up. The median EDSS decreased from 2.5 to 2.0 at the last visit ($p < 0.001$). EDSS remained stable in 5 cases, decreased by at least 0.5 point in 6 cases, and decreased by at least 1 point in 8 cases. At baseline, the mean number of gadolinium-enhancing lesions was 4.1 (range 1–20). During the follow-up, no gadolinium-enhancing lesions were detected ($p = 0.008$); 3 patients developed new T2-visible lesions at month 6 scan but the overall number of T2 lesions remained stable during the subsequent follow-up. Transient and mild side effects occurred in 8 patients.

Conclusions: Natalizumab was well-tolerated in all subjects. A strong suppression of disease activity was observed in all subjects during the follow-up.

Classification of evidence: This study provides Class IV evidence that natalizumab, 300 mg IV once every 28 days, decreased EDSS scores in pediatric patients with MS over a mean treatment period of 15.2 months. *Neurology*® 2010;75:912–917

GLOSSARY

AIFA = Agenzia Italiana del Farmaco; **EDSS** = Expanded Disability Status Scale; **GA** = glatiramer acetate; **Gd** = gadolinium; **IFN β** = interferon- β ; **MS** = multiple sclerosis; **NA** = natalizumab; **PML** = progressive multifocal leukoencephalopathy; **RR** = relapsing-remitting.

Up to 10% of multiple sclerosis (MS) cases have a disease onset before the age of 18 years.^{1–5} The majority of these subjects have a relapsing-remitting (RR) course and experience frequent relapses in the first phase of the disease, with a relapse rate that is nearly twice that of adult MS.^{6–8} The number of relapses in the first few years is a negative prognostic factor as it correlates with increased disease severity and an earlier development of the secondary progressive phase of MS.⁵

Several open studies have demonstrated that drugs active in adult MS,⁹ such as interferon- β (IFN β) and glatiramer acetate (GA), are also safe and effective in pediatric MS.⁵ For cases with a poor response to IFN β or GA and an aggressive MS evolution, other therapeutic options should be considered.

From the Multiple Sclerosis Study Center (A.G., M.Z., G.C.), Hospital of Gallarate, Gallarate; S. Andrea Multiple Sclerosis Center (C.P.), University of Rome La Sapienza, Rome; Fondazione Istituto San Raffaele “G. Giglio” (L.M.E.G.), Cefalù; Department of Neurology (V.B.M.), University of Naples, Naples; Department of Neurology (F.B.), Ospedale di Vicenza, Vicenza; U.S.D. Neurologia—Centro di Riferimento Regionale per la Sclerosi Multipla (R.C.), Spedali Civili Brescia—Presidio di Montichiari, Brescia; Multiple Sclerosis Center (M.R.), Dipartimento di Chirurgia del Sistema Nervoso e Neuroscienze, Ospedali Riuniti Bergamo, Bergamo; Department of Neurology (P.S.), Università di Perugia, Perugia; and Neuroimaging Research Unit, Institute of Experimental Neurology, Division of Neuroscience (M.F., M.A.R.), and Department of Neurology (L.M., G.C.), Hospital S. Raffaele, Milan, Italy.

Disclosure: Author disclosures are provided at the end of the article.

Natalizumab (NA) is emerging as one of the most effective treatments for adult MS, with a strong effect on clinical and MRI measures of disease activity.¹⁰ However, the occurrence of progressive multifocal leukoencephalopathy (PML) in 2 patients receiving NA in combination with IFN β -1a¹¹ brought the regulatory authorities to limit the use of NA to monotherapy as a second-line treatment. Additional PML cases have been observed during the postmarketing phase with a current estimated prevalence of 1 per 1,000 treated cases.¹²

Information on the use of NA in pediatric patients is scarce. The aim of this prospective study is to evaluate the safety profile and the effect of NA on clinical and MRI measures of disease activity in pediatric MS.

METHODS A cooperative study group to evaluate the effects of immunomodulatory drugs in children and adolescents with MS was established in 2002 in Italy including all MS centers active in the treatment of pediatric MS. In 2007, we started the collection of all incidental cases treated in Italy with NA before 18 years of age, and included in the Agenzia Italiana del Farmaco (AIFA) Registry: a form was created and used by all centers to collect complete clinical and laboratory data prospectively, at baseline and follow-up.

In line with approved guidelines for adult MS, NA was considered in 9 AIFA-approved centers in patients younger than 18 years of age because of a severe and active evolution of the disease with either 1) the demonstration of at least 2 relapses or the occurrence of a severe relapse with incomplete recovery in the previous 2 years, during treatment with IFN β or GA; or 2) the demonstration of an active MS, with at least 2 relapses in the last year and appearance of new T2 or gadolinium (Gd)-enhancing lesions on brain MRI, without any prior treatment. Fourteen patients fulfilled criterion 1, while the remaining patients fulfilled criterion 2. All patients accepted NA treatment after they and their parents had been carefully informed of related risks and advantages.

The aim of the study was to evaluate the frequency of relapses during the treatment with NA, to record modification of Expanded Disability Status Scale score (EDSS), T2, and Gd-enhancing lesions on MRI, and to collect data on adverse events.

NA was administered every 28 days according to manufacturer's guidelines. Since body weight was >50 kg in all subjects, the same dose given in adults was administered. Complete blood cell count, hepatic and renal function, as well as clinical evaluation with rating of the EDSS score¹³ were assessed monthly. In each patient, conventional brain MRI (dual-echo and postcontrast T1-weighted scans) was performed at entry and every 6 months locally using 1.5-Tesla scanners. In each center, the same scanner and a standardized MRI acquisition protocol were used for the entire study duration. The MRI sequences were positioned to run parallel to a line that joins the most inferoanterior and inferoposterior parts of the corpus callosum. On follow-up scans, obtained with the same machine and the same technical protocol, patients were carefully repositioned according to published guidelines.¹⁴ The evaluation of MRI scans was centralized at the Neuroimaging Research Unit, Hospital S. Raffaele. Gd-

enhancing lesions were identified by consensus by 2 experienced observers, blinded to patients' clinical status.¹⁵ The number of total Gd-enhancing lesions at baseline and the number of total and new Gd-enhancing lesions on follow-up scans were counted. The number of new T2-weighted lesions on follow-up scans was also assessed.

Standard protocol approvals and patient consents. The study was conducted in accordance with the International Conference on Harmonisation Guidelines of Good Clinical Practice and the Declaration of Helsinki. The protocol received approval from an ethical standards committee on human experimentation for any experiment using human subjects (ethical committee of the coordinating center). Written informed consent was obtained from each patient participating in the study (consent for research) and her or his parents.

RESULTS Nineteen subjects (12 girls) with a mean age at onset of 12.4 (SD = 2.6) years were included in the study. They received NA a mean of 27.7 (SD = 19.7) months after the onset of the disease (median 19), and after 5.2 (SD = 1.9) clinical episodes had occurred (median 6.0). The mean number of attacks in the year that preceded the treatment with NA was 3.1 (SD = 1.6) (median 2.0). The main demographic and clinical findings of each patient are reported in table 1, and the findings of the whole cohort of patients are summarized in table 2. Fourteen cases had been previously treated with other agents: IFN β (12 cases) and GA (4 cases) were stopped a mean of 38 days (range 28–70) prior to starting NA. The interval between mitoxantrone withdrawal (2 cases) and NA initiation was 16 and 36 months. Five patients with a mean EDSS = 2.2, a mean number of 2.8 relapses during the mean pretreatment period of 14 months, and a mean number of 11 Gd-enhancing lesions at baseline (median 7) did not receive any treatment before NA initiation. Patient 15, with only 2 relapses and an EDSS = 1, was treated with NA because of the high number of new T2 and Gd-enhancing lesions (>20) in 3 sequential scans, 1–2 months apart, even after a course of high-dose methylprednisolone IV.

NA administration was scheduled every 28 days, but in some cases the infusion was delayed by a few days because of fever in the previous days or school/holidays problems. A total of 15.4 (SD = 5.6) infusions (median 15) were performed during a mean follow-up of 15.2 months (median 16). Thirteen patients had a follow-up longer than 12 months (mean 18.0, median 17.0, range 13–25).

No relapses occurred in the entire cohort during the treatment with NA, and only 1 subject experienced a transitory worsening of preexisting symptoms during and immediately after the first administration of NA (no treatment required). NA was stopped for family reasons in patient 10 after 12

Table 1 Main clinical features of the 19 patients with pediatric MS receiving NA

Patient no.	Gender	Previous immunomodulatory medications	Age at MS onset, y	Pre-NA disease duration, mo	Total no. of pre-NA attacks	No. of attacks in the year prior to NA treatment	No. of NA infusions	Pre-NA EDSS	EDSS at the last observation
1	F	Rebif 22 µg, Rebif 44 µg	14	12	6	6	16	2.5	1.5
2	F	Avonex, Rebif 22 µg	12	63	8	5	17	2.5	2.0
3	F	Mitoxantrone, ^a Rebif 22 µg, Copaxone	10	59	6	2	11	5.0	4.0
4	M	Mitoxantrone, ^b Copaxone	13	19	6	3	10	2.0	1.0
5	F	Copaxone	14	15	6	5	15	1.0	0
6	F	Betaferon	14	15	5	4	14	2.0	1.5
7	F	Avonex	11	41	4	2	9	2.0	2.0
8	F	Rebif 22 µg, Betaferon, Copaxone	10	77	6	1	14	4.0	3.5
9	M	Avonex, Betaferon	14	29	6	2	13	1.5	1.5
10	F	Avonex, Rebif 22 µg	11	17	10	6	26	3.0	1.5
11	M	Avonex	6	36	6	2	11	3.5	3.0
12	M	Betaferon, Rebif 22 µg	16	14	6	5	26	3.5	2.0
13	M	Avonex, Rebif 22 µg	14	24	4	1	16	2.0	2.0
14	F	Rebif 22 µg	10	36	5	4	21	3.5	2.0
15	F	—	12	12	2	2	6	1.0	0
16	M	—	14	6	3	3	23	3.0	2.5
17	F	—	16	15	3	2	16	2.0	2.0
18	M	—	11	17	3	2	10	2.5	2.5
19	F	—	11	20	4	2	18	2.5	2.0

Abbreviations: EDSS = Expanded Disability Status Scale; MS = multiple sclerosis; NA = natalizumab.

^a Cumulative dose 30 mg/m² 36 months before NA, as induction therapy.

^b Only 1 administration, stopped because of severe lymphopenia 16 months before NA initiation.

months of treatment, but NA restarted 9 months later, after new Gd-enhancing lesions appeared.

The mean EDSS was 2.6 (SD = 1.0) before the treatment (median 2.5, range 1.0–5.0), and it decreased to 1.9 (SD = 1.0) at the last visit (median 2.0, range 0–3.5) ($p < 0.001$). EDSS remained sta-

ble in 5 cases, decreased by at least 0.5 point in 6 cases, and decreased by at least 1 point in 8 cases.

Ten adverse events (headache in 3 patients, vertigo in 2, and pharyngitis, itching, nausea, diarrhea, and fatigue each in 1 patient) were observed in 8 out of 19 patients. All the previous adverse events resolved spontaneously and no medication was required. In 3 cases, leukocyte count increased slightly, but under twice the upper normal limit, and no other hematologic abnormality was found.

At baseline, 11 pediatric MS patients had Gd-enhancing lesions (mean number of lesions 4.1, range 1–20). During the follow-up, none of the patients showed any Gd-enhancing lesions ($p = 0.008$, paired t test); only 3 patients developed new T2-visible lesions at month 6 scan (1 lesion in a patient with 7 Gd-enhancing lesions on baseline scan, 4 lesions in a patient with 7 Gd-enhancing lesions on baseline scan, and 3 lesions in a patient without Gd-enhancing lesions on the baseline scan). No new T2 or Gd-enhancing lesions were detected on the 12-month MRI scans of the 13 patients with such a

Table 2 Baseline demographic and clinical features of 19 patients with pediatric MS receiving NA

Characteristics	Mean (SD)
Age at MS onset, y	12.4 (2.6)
Pre-NA disease duration, mo	27.7 (19.7)
Age at onset of NA treatment, y	14.6 (2.2)
Weight, Kg	63 (12)
Height, cm	166 (10)
No. of attacks, including the first episode	5.2 (1.9)
No. of attacks in the year prior to NA treatment	3.1 (1.6)

Abbreviations: MS = multiple sclerosis; NA = natalizumab.

follow-up scan, and on subsequent scans for the 4 patients with a longer follow-up.

DISCUSSION In this observational Class IV study, 19 pediatric MS patients with a mean age of 14.6 years were treated with NA because of an active form of MS, as suggested by the high number of relapses after the onset of the disease and during the year that preceded NA therapy. The whole disease duration was relatively short; furthermore, the majority of the patients had MRI activity, quantified as Gd-enhancing lesions at baseline. Twelve of 14 patients experienced 2 or more relapses in the year prior to NA initiation while they were receiving a first-line treatment and, according to another study in pediatric MS,¹⁶ they were considered as nonresponders. Two patients did not fit this definition but they increased their EDSS score by ≥ 1 point after the last relapse and developed new and active brain MRI lesions. Five cases received NA as first-line treatment because of the occurrence of 2 or more relapses prior to NA treatment, rapid progression of EDSS score, and demonstration of MRI activity, with a median of 7 Gd-enhancing lesions.

After a mean follow-up of 15 months, we observed a dramatic decrease of disease activity: no relapse occurred and only 1 patient experienced a transitory worsening of preexisting symptoms during and immediately after the first administration, with spontaneous recovery. The median EDSS decreased from 2.5 to 2.0 at the end of the follow-up: it decreased by at least 0.5 in 14 cases and was unchanged in 5 patients. Brain MRI was performed every 6 months and no Gd-enhancing activity was observed.

These data suggest that disease activity was strongly suppressed in all cases for the entire follow-up duration. We could confirm, in a higher number of subjects, the positive results observed in 1 patient treated for 12 months,¹⁷ in another case treated for 15 months,¹⁸ and in 3 cases treated for 15, 16, and 24 months.¹⁹

This powerful effect of NA in reducing disease activity in pediatric MS is likely due to the predominant inflammatory pattern of the disease in this age.^{20,21} If inflammation is suppressed, the nervous tissue can be reinforced in its capability to compensate damage,²² and can be protected from irreversible brain damage, which is less severe and less diffuse at this age, compared to adult MS.^{23,24} On the other hand, recent subgroup analysis of data from the AFFIRM study support the use of NA in patients with more severe relapsing disease.²⁵ Therefore, it is not surprising to observe a great effect of NA in pediatric MS with a very high disease activity.

The favorable clinical evolution and the good tolerability of NA was confirmed in the 13 patients who

received more than 12 infusions: no relevant side effects were found, and all patients remained disease-free, according to the definition of absence of relapses and disease progression, and no new or Gd+ lesions.

The treatment was well-tolerated and well-accepted in all cases. Adverse events were recorded in 8 subjects; they were mild and transitory, and no additional medication was required. The dose of NA was the same used in adults, and it was not necessary to reduce it during the follow-up, but the reduction of NA from 5 mg/kg to 3 mg/kg of body weight is suggested if adverse events occur during the treatment.¹⁹

Cyclophosphamide has also been proposed as a second-line treatment for active pediatric MS in a retrospective study of 17 subjects with a mean age of 15 years and a mean disease duration of 3.1 years.¹⁶ EDSS score was reduced after 1 year in most cases. Three children remained relapse-free, and 12 reduced their annualized relapse rate from 3.8 to 1.6. Adverse events were frequent (nausea and vomiting in 15 patients, lymphopenia in 16, anemia in 10, alopecia in 10, menstrual disorders in 5 out of 10 girls; in rare cases, thrombocytopenia, hematuria, infections, fatigue, urticaria, and myalgias); they were severe in a few patients (amenorrhea in 3, sterility in 1, osteoporosis in 2, bladder cancer in 1). For these reasons, the authors concluded that cyclophosphamide should be considered a second-line treatment for carefully selected and monitored children with aggressive MS refractory to first-line therapies. Our data, observed in a cohort of patients with similar age, disease duration, and number of relapses prior to treatment initiation, suggest that the short-term tolerability and clinical efficacy of NA treatment are more favorable in comparison to cyclophosphamide. NA was also safe and well-tolerated in a cohort of 38 pediatric patients with Crohn disease.²⁶

A major concern of NA treatment is the possible occurrence of PML and other potential long-term adverse events such as malignancies and severe infections. Their frequency, severity, and relationship with age, disease duration, NA exposure, previous treatments, and other possible risk factors will be clarified by the many ongoing surveillance studies in adult MS. The incidence of PML increases with the duration of NA use, and it has been confirmed to be nearly 1 case per 1,000.²⁷ The median treatment duration to onset of symptoms of PML was 25 months in the 28 cases of confirmed PML reported up to November 2009.²⁷ In this cohort, only 1 patient was younger than 27 years of age. In Italy, a surveillance program has been implemented by the Regulatory Authority. So far, no relevant side effects have been recorded in more than 2,000 patients with adult-onset MS treated with NA.²⁸ The small number of

our pediatric patients with MS does not allow definition of the safety profile of NA in children. Further multinational long-term studies are required to clarify definitively if virus exposure during late childhood–early adolescence²⁹ involves a different risk of PML. If risks will be acceptable, NA could become the first-choice agent for second-line treatment in selected children and adolescents with active MS, due to its overall good tolerability, easy regimen of administration, and efficacy.

An open question in pediatric MS is how long to continue the treatment with NA: most subjects had been previously treated with first-line, and sometimes with other second-line agents, without sufficient benefit: if safety data will be reassuring, NA could be continued, with a careful monitoring of adverse events. Our study group plans to continue long-term follow-up of patients included in this study, and to enroll new subjects treated with NA in our database, in order to help clarify these issues.

COINVESTIGATORS

Luca Prosperini, MD (S. Andrea Multiple Sclerosis Center, University of Rome La Sapienza, Site Investigator); Giovanna Borriello, MD (S. Andrea Multiple Sclerosis Center, University of Rome La Sapienza, Site Investigator); Anna Lisa Rizzo, MD (Centro Studi Sclerosi Multipla, Hospital of Gallarate, Site Investigator); Gaetano Vitello, MD (Fondazione Istituto San Raffaele “G.Giglio,” Cefalù, Site Investigator).

DISCLOSURE

Dr. Ghezzi has served on scientific advisory boards for Merck Serono and Teva Pharmaceutical Industries Ltd.; has received speaker honoraria from Bayer Schering Pharma, Biogen-Dompè AG, Merck Serono, and Novartis; has served as a consultant for Actelion Pharmaceuticals Ltd., Merck Serono, and Novartis; and has received support to participate in National and International Congresses from Biogen-Dompè AG, Bayer Schering Pharma, Merck Serono, and Sanofi-Aventis. Prof. Pozzilli has served on scientific advisory boards for Novartis, Merck Serono, Biogen-Dompè AG, and Bayer Schering Pharma; has received funding for travel and speaker honoraria from Sanofi-Aventis, Biogen-Dompè AG, Bayer Schering Pharma, and Novartis; and receives research support from Merck Serono and Sanofi-Aventis. Dr. Grimaldi serves on a scientific advisory board for Merck Serono; has received funding for travel or speaker honoraria from Merck Serono, Biogen-Dompè AG, Sanofi-Aventis, Bayer Schering Pharma, and Solvay Pharmaceuticals, Inc.; receives institutional research support from Teva Pharmaceutical Industries Ltd., Biogen Idec, Genzyme Corporation, Sanofi-Aventis, Merck Serono, Novartis, and Eisai Inc.; and receives research support from Merck Serono, Biogen-Dompè AG, and Ministero della Salute. Dr. Brescia-Morra has received funding for travel, speaker honoraria, and research support from Sanofi-Aventis, Bayer Schering Pharma, Merck Serono, and Biogen-Dompè AG. Dr. Bortolon has received support to participate in National and International Congresses from Biogen-Dompè AG, Bayer Schering Pharma, Merck Serono, and Sanofi-Aventis. Dr. Capra has served on a scientific advisory board for Novartis, and received speaker honoraria from Bayer Schering Pharma, Biogen-Dompè AG, and Sanofi-Aventis. Dr. Filippi serves on scientific advisory boards for Teva Pharmaceutical Industries Ltd. and Genmab A/S; has received funding for travel from Bayer Schering Pharma, Biogen-Dompè AG, Genmab A/S, Merck-Serono, and Teva Pharmaceutical Industries Ltd.; serves on editorial boards of the *American Journal of Neuroradiology*, *BMC Musculoskeletal Disorders*, *Clinical Neurology and Neurosurgery*, *Erciyes Medical Journal*, *Journal of Neuroimaging*, *Journal of Neurology Neurosurgery and Psychiatry*, *Journal of Neurovirology*, *Magnetic Resonance Imaging*, *Multiple Sclerosis*, and *Neurological Sciences*;

serves as a consultant to Bayer Schering Pharma, Biogen-Dompè AG, Genmab A/S, Merck-Serono, Peppen Corporation, and Teva Pharmaceutical Industries Ltd.; serves on speakers' bureaus for Bayer Schering Pharma, Biogen-Dompè AG, Genmab A/S, Merck-Serono, and Teva Pharmaceutical Industries Ltd.; and receives research support from Bayer Schering Pharma, Biogen-Dompè AG, Genmab A/S, Merck-Serono, Teva Pharmaceutical Industries Ltd., Fondazione Italiana Sclerosi Multipla, and Fondazione Mariani. Dr. Moiola has received support to participate in National and International Congresses from Biogen-Dompè AG, Bayer Schering Pharma, Merck Serono, and Sanofi-Aventis. Dr. Rocca reports no disclosures. Dr. Rottoli has received support to participate in National and International Congresses from Biogen-Dompè AG, Bayer Schering Pharma, Merck Serono, and Sanofi-Aventis. Dr. Sarchielli has received support to participate in National and International Congresses from Biogen-Dompè AG, Bayer Schering Pharma, Merck Serono, and Sanofi-Aventis. Dr. Zaffaroni has served on scientific advisory boards for Teva Pharmaceutical Industries Ltd. and Medtronic, Inc.; has served as a consultant for and received support to participate in National and International Congresses from Biogen-Dompè AG, Bayer Schering Pharma, Merck Serono, and Sanofi-Aventis; and serves on the editorial advisory board of *Multiple Sclerosis International*. Prof. Comi has served on scientific advisory boards for Teva Pharmaceutical Industries Ltd., Sanofi-Aventis, Merck Serono, Bayer Schering Pharma, and Biogen Dompè AG; and has received speaker honoraria from Teva Pharmaceutical Industries Ltd., Sanofi-Aventis, Serono Symposia International Foundation, Biogen-Dompè AG, Merck Serono, and Bayer Schering Pharma.

Received January 12, 2010. Accepted in final form May 20, 2010.

REFERENCES

1. Ghezzi A, Deplano V, Faroni J, et al. Multiple sclerosis in childhood: clinical features of 149 cases. *Mult Scler* 1997; 3:43–46.
2. Boiko A, Vorobeychik G, Paty D, et al. Early onset multiple sclerosis: a longitudinal study. *Neurology* 2002;59: 1006–1010.
3. Simone IL, Carrara D, Tortorella C, et al. Course and prognosis in early-onset MS: comparison with adult-onset forms. *Neurology* 2002;59:1922–1928.
4. Renoux C, Vukusic S, Mikaeloff Y, et al. Natural history of multiple sclerosis with childhood onset. *N Engl J Med* 2007;365:2603–2613.
5. Banwell B, Ghezzi A, Bar-Or A, et al. Multiple sclerosis in children: clinical diagnosis, therapeutic strategies, and future directions. *Lancet Neurol* 2007;6:887–902.
6. Ghezzi A, Pozzilli C, Liguori M, et al. Prospective study of multiple sclerosis with early onset. *Mult Scler* 2002;8:115–118.
7. Gusev E, Boiko A, Bikova O, et al. The natural history of early onset multiple sclerosis: comparison of data from Moscow and Vancouver. *Clin Neurol Neurosurg* 2002; 104:203–207.
8. Gorman MP, Healy BC, Polgar-Turcsanyi M, Chitnis T. Increased relapse rate in pediatric-onset compared with adult-onset multiple sclerosis. *Arch Neurol* 2009;66:54–59.
9. Goodin DS, Frohman EM, Garmany GP, et al. Disease modifying therapies in multiple sclerosis: Subcommittee of the American Academy of Neurology and the MS Council for Clinical Practice Guidelines. *Neurology* 2002;58:169–178.
10. Polman CH, O'Connor PW, Havrdova E, et al. A randomized, placebo-controlled trial of Natalizumab for relapsing multiple sclerosis. *N Engl J Med* 2006;354: 899–910.
11. Yousry TA, Major EO, Ryschkewitsch C, et al. Evaluation of patients treated with natalizumab for progressive

- multifocal leukoencephalopathy. *N Engl J Med* 2006; 354:924–933.
12. Kappos L, Bates D, Hartung HP, et al. Natalizumab treatment for multiple sclerosis: recommendations for patient selection and monitoring. *Lancet Neurol* 2007;6:431–441.
 13. Kurtzke JF. Rating neurological impairment in multiple sclerosis: an expanded disability status scale. *Neurology* 1983;33:1444–1452.
 14. Miller DH, Barkhof F, Berry I, et al. Magnetic resonance imaging in monitoring the treatment of multiple sclerosis: concerted action guidelines. *J Neurol Neurosurg Psychiatry* 1991;54:683–688.
 15. Filippi M, Gawne-Cain ML, Gasperini C, et al. Effect of training and different measurement strategies on the reproducibility of brain MRI lesion load measurements in multiple sclerosis. *Neurology* 1998;50:238–244.
 16. Makhani N, Gorman MP, Branson HM, et al. Cyclophosphamide therapy in pediatric multiple sclerosis. *Neurology* 2009;72:2076–2082.
 17. Boriello G, Prosperini L, Lucchetti A, Pozzilli C. Natalizumab treatment in pediatric multiple sclerosis: a case report. *Eur J Paediatr Neurol* 2009;13:67–71.
 18. Appleton RE, Boggild M. Natalizumab in paediatric multiple sclerosis and service implication. *Dev Med Child Neurol* 2009;51:758–759.
 19. Huppke P, Stark W, Zurcher C, et al. Natalizumab in paediatric multiple sclerosis and service implication. *Arch Neurol* 2008;65:1655–1658.
 20. Chabas D, Castello-Trivino T, Mowry EM, et al. Vanishing MS T2-bright lesions before puberty: a distinct MRI phenotype. *Neurology* 2008;71:1090–1093.
 21. Waubant E, Chabas D, Okuda D, et al. Difference in disease burden and activity in pediatric patients on brain magnetic resonance imaging at time of multiple sclerosis onset vs adults. *Arch Neurol* 2009;66:967–971.
 22. Rocca MA, Absinta M, Ghezzi A, et al. Is a preserved functional reserve a mechanism limiting clinical impairment in pediatric MS patients? *Hum Brain Mapp* 2009;30:2844–2851.
 23. Tortorella P, Rocca MA, Mezzapesa DM, et al. MRI quantification of gray and white matter damage in patients with early-onset multiple sclerosis. *J Neurol* 2006;253:903–907.
 24. Mesaros S, Rocca MA, Absinta M, et al. Evidence of thalamic gray matter loss in pediatric multiple sclerosis. *Neurology* 2008;70:1107–1112.
 25. Hutchinson M, Kappos L, Calabresi PA, et al, for the AFFIRM and SENTINEL Investigators. The efficacy of natalizumab in patients with relapsing multiple sclerosis: subgroup analysis of AFFIRM and SENTINEL. *J Neurol Epub* 2009 Mar 18.
 26. Hyams JS, Wilson DC, Thomas A, et al. Natalizumab therapy for moderate to severe Crohn disease in adolescents. *J Pediatr Gastroenterol Nutr* 2007;44:185–191.
 27. Clifford BD, DeLuca A, Simpson DM, et al. Natalizumab-associated progressive multifocal leukoencephalopathy in patients with multiple sclerosis: lessons from 28 cases. *Lancet Neurol* 2010;9:438–446.
 28. Tedeschi G, Amato MP, D'Alessandro R, et al. The pharmacovigilance program on natalizumab in Italy: 2 years of experience. *Neurol Sci* 2009;30(suppl 2):S163–S165.
 29. Sweet TM, Del Valle L, Khalili K. Molecular biology and immunoregulation of human neurotropic JC virus in CNS. *J Cell Physiol* 2002;191:249–256.

Apply Now for a 2011 Clinical Research Training Fellowship in Neurology

The AAN Foundation is now accepting applications for six Clinical Research Training Fellowships in neurology for 2011, including a new award in epilepsy research. Fellowships provide recipients with salary and tuition stipends, allowing them protected time to complete clinical research projects and take the next step toward a career in neurologic research. Applications are due by Friday, October 1, 2010. Apply online at www.aan.com/fellowship by October 1, 2010. For more information, contact Terry Heinz at theinz@aan.com or (651) 695-2746.

Safety and efficacy of natalizumab in children with multiple sclerosis

A. Ghezzi, C. Pozzilli, L.M.E. Grimaldi, et al.

Neurology 2010;75;912

DOI 10.1212/WNL.0b013e3181f11daf

This information is current as of May 2, 2012

Updated Information & Services	including high resolution figures, can be found at: http://www.neurology.org/content/75/10/912.full.html
References	This article cites 28 articles, 14 of which can be accessed free at: http://www.neurology.org/content/75/10/912.full.html#ref-list-1
Citations	This article has been cited by 2 HighWire-hosted articles: http://www.neurology.org/content/75/10/912.full.html#related-urls
Subspecialty Collections	This article, along with others on similar topics, appears in the following collection(s): All Pediatric http://www.neurology.org/cgi/collection/all_pediatric Clinical trials Observational study (Cohort, Case control) http://www.neurology.org/cgi/collection/clinical_trials_observational_study_cohort_case_control Multiple sclerosis http://www.neurology.org/cgi/collection/multiple_sclerosis
Permissions & Licensing	Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: http://www.neurology.org/misc/about.xhtml#permissions
Reprints	Information about ordering reprints can be found online: http://www.neurology.org/misc/addr.xhtml#reprintsus

