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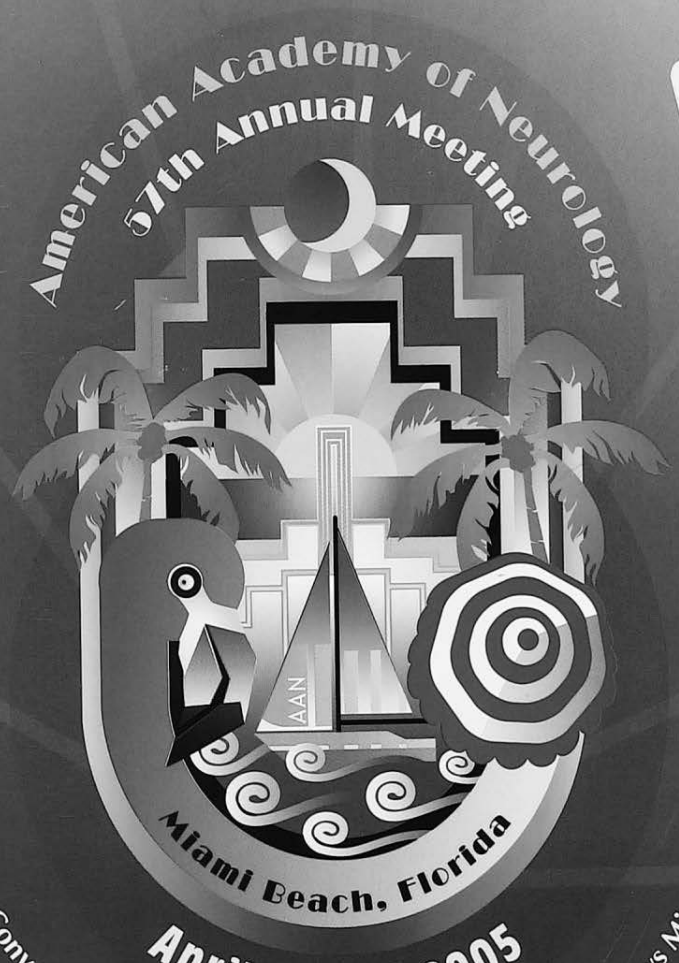
57TH ANNUAL MEETING PROGRAM



Miami Beach Convention Center • Fontainebleau Hilton Resort • Loews Miami Beach Hotel

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1:30 PM

A Double-Blind, Placebo-Controlled, Multicenter Study To Assess the Safety and Efficacy of AVP-923 (Dextromethorphan/Quinidine) in the Treatment of Pseudobulbar Affect in Patients with Multiple Sclerosis

Hillel Panitch, Burlington, VT, Ronald A. Thisted, Chicago, IL, Laura E. Pope, James E. Berg, San Diego, CA

OBJECTIVE: The objective was to evaluate the safety, tolerance, and efficacy of AVP-923 (capsules containing dextromethorphan hydrobromide [DM; 30 mg] and quinidine sulfate [Q; 30 mg]), compared with placebo, for the treatment of pseudobulbar affect (PBA) in patients with multiple sclerosis (MS). **BACKGROUND:** PBA is associated with various neurological disorders and is characterized by uncontrollable episodes of laughing and/or crying out-of-proportion to, or incongruent with, underlying mood. Q is included in the formulation as a CYP2D6 inhibitor to block the rapid first-pass metabolism of DM and increase its pharmacological potential. **DESIGN/METHODS:** MS patients at 22 community and university based centers were randomized to receive AVP-923 (n=76) or placebo (n=74) twice daily (q12h) for 12 weeks. Each patient completed a diary recording daily the number of laughing and/or crying episodes, medication schedule, and adverse events (AEs). Patients returned to the clinic an Days 15, 29, 57, and 85 for evaluation. PBA was assessed during the clinic visits using a validated self-assessment tool referred to as the CNS-LS. The study enrolled adult male and female patients with MS who scored ≥13 on the CNS-LS. Safety measures were AEs, clinical chemistry, vital signs, physical examinations and ECGs. The primary efficacy analysis compared the change in CNS-LS score between the AVP-923 and placebo groups, where individual change was the difference between the baseline and the average of the Day 15, 29, 57 and 85 study visits. Secondary endpoints included a comparison of the number of episodes of laughing and/or crying, a visual analog scale (VAS) score for overall quality of life, a VAS score for quality of relationships and a pain intensity rating scale score. **RESULTS:** Patients receiving AVP-923 had a clinically and statistically greater reduction in CNS-LS than those receiving placebo ($p<0.0001$). All 4 secondary endpoints were also statistically significant in favor of AVP-923: number of laughing and crying episodes ($p=0.0002$); quality of life ($p<0.0001$), quality of relationships ($p=0.0001$); and pain reduction ($p=0.027$). Additional analysis revealed that nearly twice as many AVP-923 subjects as placebo subjects responded to treatment (84% vs 49%; $p<0.0010$), that the number of episodes per week was reduced 46% in the AVP-923 group compared to the placebo group and that treatment effects were observed as early as the first week of treatment. The nature, frequency and intensity of AEs were within acceptable limits, and were similar between groups. Dizziness was observed more frequently in the AVP-923 group ($p=0.01$). Eleven AVP-923 patients (14%) and 8 placebo patients (11%) had AEs resulting in discontinuation. There were no clinically significant changes observed in other safety measures. **CONCLUSIONS:** AVP-923 was safe, well-tolerated, and highly effective in treating pseudobulbar affect in patients with MS.

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S46.002

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Ginkgo Biloba Improves Cognitive Performance in Multiple Sclerosis Patients with Cognitive Dysfunction: A Pilot Study

Bridget Bagert, Boston, MA, Jesus Lovera, Barry Oken, Portland, OR, Kyle Smoot, Seattle, WA, Katherine Wild, Rachel Frank, Kristin Bogardus, Dennis Bourdette, Portland, OR

OBJECTIVE: To determine if multiple sclerosis (MS) subjects with cognitive impairment treated with ginkgo biloba (GB) improve their performance on a neuropsychological test battery as compared to placebo treated subjects. **BACKGROUND:** Cognitive dysfunction is a major cause of disability in MS, and presently there is no effective treatment. One agent that may have some benefit is GB, which many MS patients use despite a paucity of existing evidence to support such use. **DESIGN/METHODS:** This was a two-arm, parallel design, randomized, double-blind placebo-controlled, trial in MS patients with cognitive impairment. Subjects had to have definite MS and demonstrate cognitive dysfunction on the Paced Auditory Serial Addition Test (PASAT) on the Oxford Neuropsychological Battery. Subjects were excluded. Eligible subjects also underwent the following tests: Stroop Color Word Test; Controlled Oral Word Association Test; Symbol Digit Modalities Test; adapted Useful Field of Vision Test. Subjects underwent three neuropsychological test batteries over a five week period to minimize learning effects. The third test battery served as the baseline. Subjects were then randomized to receive either GB (120 mg twice a day) or placebo for 12 weeks. Platelet function analyses (PFA) were performed at baseline and exit since GB has been reported to impair platelet function. ANCOVA was used to compare the two groups with baseline performance in each of the cognitive tests, gender, EDSS, time since onset and baseline BDI included as covariates. For the PFA results at exit, baseline PFA results were the only covariate included. **RESULTS:** Thirty-nine subjects completed the study, 20 received GB and 19 placebo. There were no significant differences between the groups on gender, age, education, type of MS, years since onset, or baseline performance on the neuropsychological tests. There was a significant difference between the groups at exit on the Stroop Test ($p=0.02$). At baseline the means were 29.56 sec for the placebo group and 31.84 sec for GB. At exit the GB group improved to 24.63 sec while the placebo group was essentially unchanged at 30.22 sec. There were no significant differences between groups on other tests. There were no significant side-effects in either group and no significant difference at exit in PFA. The baseline PFA with epinephrine mean for placebo was 123.0 sec and for GB 120.5 sec and at exit 126.1 sec for the placebo group and 86.7 sec for the GB group. **CONCLUSIONS:** This pilot trial suggests that GB may be effective in improving attention in MS patients with cognitive dysfunction. GB did not alter platelet function or cause significant side-effects. Definitive investigation should be pursued.

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S46.003

2:00 PM

An Open-Label, Prospective Study of Oral Fumaric Acid Therapy for the Treatment of Relapsing-Remitting Multiple Sclerosis (RRMS)

S. K. Schimrigk, N. Brune, K. Hellwig, M. Rieks, V. Hoffmann, D. Pohlau, H. Przuntek, Bochum, Germany

OBJECTIVE: To evaluate the safety and efficacy of oral fumaric acid in patients with RRMS. **BACKGROUND:** Fumaric acid is an effective and safe therapy for psoriasis. Since the inflammatory processes involved in multiple sclerosis (MS) are thought to be similar to those of psoriasis, fumaric acid therapy may also be effective in treating MS. **DESIGN/METHODS:** An exploratory, prospective, open-label study of oral fumaric acid esters was conducted in patients with RRMS. The study consisted of four phases, a 6-week baseline, an 18-week treatment at a target dose of 720 mg per day, a 4-week washout, and a second 70-week treatment phase at a target dose of 360 mg per day. All patients were treated with oral fumaric acid ester therapy. The dose was slowly titrated up to the target dose over 9 weeks in the 1st treatment period. Patients started at the target dose in the second treatment phase. All patients had Gadolinium enhancing lesions on baseline Brain MRI. Safety was assessed by physical and neurologic exams, blood chemistry/hematology, electrocardiogram, and urinalysis. The primary efficacy outcomes were the number and volume of gadolinium-enhancing (Gd+) lesions on serial T1-weighted magnetic resonance imaging (MRI) scans. Clinical outcomes included Expanded Disability Status Scale (EDSS) score, ambulation index (AI), and nine-hole peg test (9-HPT). The effects of fumaric acid on intercellular cytokine profiles, T-cell apoptosis, and soluble adhesion molecule (sICAM-1) were also assessed. **RESULTS:** Of 10 enrolled in the study, 3 patients discontinued during the first 3 weeks of treatment. Six of 7 patients initially experienced mild to moderate gastrointestinal discomfort, which decreased gradually in all patients. All other side effects were generally mild and transient. Fumaric acid therapy significantly reduced the number ($p<0.05$) and volume ($p<0.01$) of Gd+ lesions from baseline after 12 weeks of treatment. EDSS scores, AI, and 9-HPT remained stable or slightly improved from baseline in all patients. A highly significant increase in CD4+ cells producing interleukin (IL)-10, IL-4, and TGF-beta was observed during treatment compared with baseline and post-study periods. A 50% increase in the rate of apoptosis in T-helper (TH) cells was observed after 6 weeks of treatment and declined to baseline levels after an addition 6 weeks of treatment. No significant changes in intercellular TH1-type cytokine production was observed while serum levels of sICAM-1 were significantly decreased. **CONCLUSIONS:** Fumaric acid significantly reduced the number and volume of Gd+ lesions over 70 weeks of treatment, and all patients were clinically stable throughout the study. No serious adverse events were reported. Data on immunologic parameters suggest that fumaric acid causes a bystander suppression pattern toward a predominantly TH2-type cytokine profile. These findings suggest that further study of oral fumaric acid for the

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S46.004

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A Phase I Trial of CTLA4Ig Treatment in MS

Samia J. Khoury, Vissia Viglietta, Guy Buckle, David Hafler, Boston, MA, Kasia Bourcier, Bethesda, MD, Charles Guttmann, Michelle Bikowski, Boston, MA, James Rusche, Hal Landy, James McNally, Karen Jauregui, Waltham, MA

OBJECTIVE: To determine the safety of RG2077 in patients with multiple sclerosis. **BACKGROUND:** Multiple sclerosis (MS) is an autoimmune disease of the central nervous system initiated by autoreactive CD4+ T cells, which recognize and respond to myelin antigens. T cell activation depends on signals delivered through the T cell receptor and co-stimulation via CD28-CD80/CD86 interactions. CTLA4-Ig has been used to block CD28-CD80/86 costimulation in several animal models of autoimmune disease, with improvement in disease manifestations. Previous studies using another CTLA4Ig agent have shown clinical benefit in psoriasis and rheumatoid arthritis. RG2077 (Repligen) is a recombinant protein of CTLA4 (cytolytic-T-lymphocyte associated antigen-4) fused to the heavy chain constant region of the human immunoglobulin of the IgG4 isotype. The gene sequence encoding the immunoglobulin portion has been altered to remove the functional properties of binding the Fc receptor and fixation of complement. **DESIGN/METHODS:** We performed an open-label, dose escalation study of RG2077 in relapsing-remitting MS patients. Each subject received a single infusion of RG2077 in the one of the following dosage groups: 2.0 mg/kg (n = 4), 10.0 mg/kg (n = 4), 20.0 mg/kg (n = 4) and 35.0 mg/kg (n = 4). Safety assessments included blood studies, a MRI, a neurological examination and physical examination. Mechanistic studies were performed at baseline, 1 week, 1 month and 3 months post infusion. Safety data on the first 2 dose groups were presented at the AAN in 2004. The study was supported by the Immune Tolerance Network. **RESULTS:** We are currently dosing the 35.0 mg/kg cohort, and the last follow up visit is expected in March '05. No major adverse events have been observed to date. Immunologic/mechanistic studies have been performed and show evidence of biologic activity. The results of the safety data and analysis of the immunologic effects of the treatment on the whole study cohort will be presented. **CONCLUSIONS:** CTLA4Ig treatment appears to be safe for MS patients.

Supported by: The Immune Tolerance Network

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Immunoablation Followed by Autologous Stem Cell Transplantation as a Treatment for Aggressive Multiple Sclerosis: 3 Year Follow-Up of the First 6 Patients

Mark S. Freedman, Harold L. Atkins, Guylaine Theoret, Ottawa, ON, Canada, and The Canadian MS BMT Study Group

OBJECTIVE: To report on the progress of the Canadian MS bone marrow transplant (BMT) study by providing clinical data on the first 6 patients reaching the final 3 year endpoint. **BACKGROUND:** We hypothesized that complete ablation of the immune system will halt any ongoing MS immune mediated damage to the CNS and that reconstituting an immune system derived from hematopoietic stem cells will not result in re-development of might facilitate endogenous repair mechanisms, or that repair comes directly from the transplanted stem cells that have the capacity to become CNS cells. The first six patients are now 3 years out from this procedure and this report deals with their clinical and functional outcomes. **DESIGN/METHODS:** The Canadian BMT trial is a non-randomized phase II trial of immunoablation and autologous hematopoietic T cell-depleted stem cell transplantation (ASCT) for MS patients deemed to have early aggressive disease and who have failed contemporary treatment. Immunoablation was carried out using busulphan (16 mg/kg), cyclophosphamide (200 mg/kg) and rabbit ATG (5mg/kg). Patients were followed and assessed every 3 months by both 'treating' and 'blinded' evaluators. Clinical evaluations included the EDSS and MSFC functional scales as well as depression and quality of life measures. **RESULTS:** By the time of presentation most of these patients will have completed nearly 36 months of follow-up and their clinical data will be presented. One of these first six patients is a 'control' patient, who met the same rigid inclusion/exclusion criteria of the treated patients, but chose not to undergo the full procedure. This individual was followed in the same manner as the transplanted patients, but received only 'best medical care', which entailed the use of mitoxantrone. Thus far, no clinical attack has occurred in over 230 months of follow-up of 11 transplanted patients. Functional scales demonstrate either stability or improvement in a number of measures. In some cases, vision recovered substantially, while in others there were marked improvements in pyramidal/cerebellar KFS or overall EDSS. In addition to reviewing EDSS and MSFC scoring, we will present the results of validated quality of life questionnaires completed prospectively over the same time frame. MRI study results will be presented in a companion abstract, but similarly failed to detect any new activity in any patient. **CONCLUSIONS:** Immunoablation and ASCT results in clinical stabilization or improvement in this very aggressive form of MS for up to 3 years. Some patients have actually seen some improvement in terms of their motor and visual capabilities, raising the possibility that the treatment does more than simply stop ongoing disease activity.

Supported by: Multiple Sclerosis Foundation of Canada

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S46.006

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Evidence for Acute Brain "Pseudo-Atrophy" after Treating MS with Immunoablation Followed by Autologous Stem Cell Transplantation

Jacqueline T. Chen, Donald L. Collins, Montreal, QC, Canada, Mark S. Freedman, Harold L. Atkins, Ottawa, ON, Canada, the Canadian MS BMT Study Group, Douglas L. Arnold, Montreal, QC, Canada

OBJECTIVE: To assess the effect of stopping inflammation on the evolution of brain atrophy in patients with multiple sclerosis (MS). **BACKGROUND:** Brain atrophy is usually considered a biomarker of neurodegeneration and loss of brain tissue. However, fluid shifts and other factors can acutely alter brain volume. Pseudo-atrophy due to the resolution of inflammatory edema has been proposed as a factor contributing to loss of brain volume after initiation of therapy in MS. To test this hypothesis, we measured the rate of atrophy in patients with very aggressive, active MS before and after stopping inflammation with immunoablation that was performed prior to autologous stem cell transplantation (ASCT). **DESIGN/METHODS:** Brain MRI was performed at baseline (-2.5 mo and -0.5 mo) and post-immunoablation (+1 mo, +4 mo, +6 mo, +9 mo, +12 mo), in five patients with secondary-progressive MS. Quantification of brain atrophy was performed on T1w MRI using SIENA. Gadolinium-enhancing lesions were also quantified. **RESULTS:** At baseline, 4 of 5 patients had gadolinium enhancing lesions (14±8 lesions/subject). Over a 2-month interval prior to immunoablation, the rate of atrophy was small and heterogeneous within the group (mean±SD = −0.79±3.47 %/yr, p=0.64). The rate of atrophy dramatically increased over the subsequent 4 months during which the patients received immunoablative doses of chemotherapy and ASCT (8.65±2.60 %/yr (p=0.003)). In some patients, the rate of atrophy stabilized by 1 month post-transplant. In other patients, the rate of atrophy stabilized after 4–6 months. **CONCLUSIONS:** Immunoablation followed by ASCT was associated with an acute increase in the rate of atrophy. The rate of atrophy (approximately 3% over 4 months) was larger than what one would normally expect due to loss of tissue, even in this aggressive group of MS patients. These preliminary data, therefore, support the hypothesis that stopping inflammation in MS can be associated with "pseudo-atrophy".

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