Highlights of the 54th Annual Meeting of the American Academy of Neurology

by Lawrence M. Prescott, PhD

Denver, Colorado was the venue for the 54th Annual Meeting of the American Academy of Neurology, where more than 8,000 neurologists, neuroscientists, and other health care professionals from a variety of disciplines gathered from April 13 to 20, 2002 to hear the latest developments in the prevention, treatment, and control of neurologic diseases. Major areas of interest included new approaches with established drugs for the treatment of refractory multiple sclerosis; neuropsychiatric complications of Parkinson’s disease; and migraine prophylaxis in children and adolescents; as well as the development of novel drugs for the treatment of painful diabetic neuropathy and chronic motor-incomplete spinal cord injury. Listed below are highlights of these presentations.

Combination Therapy for Relapsing–Remitting MS

**Speaker:** Silva Markovic-Plese, MD, Clinical Fellow, Neuroimmunology Branch, the National Institute of Neurological Diseases and Stroke, National Institutes of Health, Bethesda, Maryland.

Interferon beta-1b (INF-beta-1b) (Betaseron, Berlex) and azathioprine (Imuran, Prometheus) combination therapy appears to offer an effective treatment approach in patients with relapsing–remitting multiple sclerosis (RRMS) who are refractory to treatment with INF beta-1b alone.

To reach this conclusion, a study was carried out to assess the effectiveness of azathioprine in augmenting the response to INF beta-1b in a group of patients with RRMS. This group of individuals continued to have active disease while being maintained on INF beta-1b monotherapy. To this end, a subset of six patients refractory to INF beta-1b therapy was identified from a longitudinal study of RRMS patients treated with INF beta-1b. These patients had been treated with INF beta-1b for three to 35 months (median: 17 months), with continuously high disease activity (median: 12.69; Gadolinium [Gd]-enhancing lesions and median exacerbation rate, 1.63). The six patients were studied on INF beta-1b 8 IMU subcutaneously on alternate days and oral azathioprine 1.5 mg/kg daily for six to 48 months (median: 15 months). Patients were evaluated monthly with serial magnetic resonance imaging (MRI) scans and comprehensive neurological evaluations.

The number of Gd-enhancing MRI lesions was used as a primary outcome measure. Clinical outcome measures (expanded disability status score (EDSS), progression index [change in EDSS per year], and exacerbation rates).

In this group of patients, adding azathioprine to INF beta-1b therapy resulted in a reduction of new Gd-enhancing lesions from 6.83 to 3.37. Also, the number of total Gd-enhancing lesions was reduced from 12.67 to 3.87 during the combination therapy, compared to INF beta-1b monotherapy. Both of these reductions between combination therapy and baseline were statistically significant. Thirteen months after the addition of azathioprine to INF beta-1b, complete clinical responses were reported. At four years’ follow-up (one patient had been followed for eight years), the patients, four of whom had recurrent exacerbations during INF beta-1b monotherapy, had a sharp reduction in the number of relapses during the combination therapy, and all were, for the most part, exacerbation-free.

Cholinesterase Inhibitor for Parkinsonian Neuropsychiatric Symptoms

**Speaker:** Paul Reading, PhD, Clinical Neurologist, Department of Neurology, Newcastle General Hospital, Newcastle-Upon-Tyne, United Kingdom.

Results from an open-exploratory study point out that the cholinesterase inhibitor rivastigmine (Exelon, Novartis) has a positive effect on the neuropsychiatric complications of Parkinson’s disease (PD), particularly hallucinations and sleep disturbances, and significantly enhances cognitive performance without worsening motor control.

To reach these conclusions, a group of 12 patients with established PD, troublesome hallucinations, and moderate cognitive impairment were enrolled in a 17-week study. The patients underwent eight weeks of titration with rivastigmine to the highest tolerated dose, and were given the drug at that dose for six weeks, after which time the treatment was withdrawn. Cognitive performance was measured by the MMSE (Mini-Mental State Examination) and a computerized neuropsychological battery, the CDR battery (Cognitive Drug Research). Neuropsychiatric symptoms and their effects on the caregiver were assessed with the NPI (Neuropsychiatric Inventory). Motor disability was recorded using the UPDRS (Unified Parkinson’s Disease Rating Scale).

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Neuropsychiatric symptoms and the distress they caused to caregivers, as measured by the NPI, were successfully treated with rivastigmine; patients with hallucinations and sleep disturbances were particularly sensitive to the drug. Cognitive performance measured by the MMSE and CDR battery was also significantly enhanced. There was a non-significant tendency for improvement in motor UPDRS scores. Overall, the drug was well-tolerated.

Acetylcholinesterase Inhibitor For Vascular Dementia

**Speaker:** Raymond D. Pratt, MD, Senior Director and Therapeutic Head, CNS & Internal Medicine, Clinical Research & Development, Eisai Inc., Teaneck, New Jersey.

Findings from a combined analysis of two 24-week, double-blind, randomized, placebo-controlled studies pointed out that donepezil (Aricept, Pfizer/Eisai Inc.), an acetylcholinesterase inhibitor presently indicated for Alzheimer’s disease, significantly improved cognition in patients with both possible and probable vascular dementia.

A total of 1,219 patients with probable (873 patients) or possible (326 patients) vascular dementia, according to NINDS-AIREN (National Institute of Neurological Diseases and Stroke—Association International pour le Recherche et l’Enseignement en Neurosciences) criteria, were enrolled into the two studies and randomly assigned to receive placebo, donepezil 5 mg, or donepezil 10 mg daily (5 mg for the first 28 days), for 24 weeks. In these patients, donepezil treatment, either 5 or 10 mg, resulted in beneficial treatment effects on cognition from week six onward, as assessed by the Alzheimer’s Disease Assessment Scale–cognitive subscale (ADAS-cog). The results obtained using the Mini-Mental State Examination (MMSE), a measure of cognitive function, confirmed the significant benefits of donepezil treatment on cognition, with significant improvements from baseline scores. In patients administered donepezil 10 mg/day, a greater improvement in cognition was shown in those with probable vascular dementia than among those with possible vascular dementia. In an assessment of global function, a significantly larger number of patients with probable vascular dementia demonstrated improvement on donepezil, compared to placebo, as measured by the Clinician’s Interview-Based Impression of Change–plus (CIBIC-plus). Also, in patients with possible vascular dementia, a greater proportion of those on donepezil demonstrated improvement or no change, compared to placebo, as measured by CIBIC-plus. Overall, although results from this analysis indicate that the rates of cognitive decline might vary somewhat in probable and possible vascular dementia, donepezil is nevertheless an effective treatment for the cognitive symptoms of both possible and probable vascular dementia.

Antiepileptic for Pediatric and Adolescent Migraine Prophylaxis

**Speaker:** Jose Ferreira, MD, Pediatric Epilepsy Neurologist, Pediatric Epilepsy and Neurology Specialists, Tampa, Florida.

Topiramate (Topamax, Ortho-McNeil), a broad-spectrum antiepileptic, appears to be efficacious and generally well-tolerated in pediatric and adolescent migraine prophylaxis, substantially reducing migraine headache frequency and severity and improving the disability associated with migraine.

Because present-day mainstays of migraine prophylaxis (calcium channel blockers, beta-blockers, antidepressants, and divalproex sodium) might have limited efficacy and could be poorly tolerated, and topiramate is known to exhibit several mechanisms of action that contribute to migraine prevention, a retrospective analysis was conducted to determine the efficacy of topiramate in the treatment of pediatric and adolescent patients diagnosed with migraine and chronic daily headaches.

A chart review was performed for pediatric and adolescent patients who had been treated with topiramate for migraine. Thirty-four patients (10 male, 24 female), with a mean age of 14 years (range: 8–19 years) had been diagnosed with migraine (16 patients), daily headache (17 patients), and headaches associated with hydrocephalus (1 patient). Most patients had been started with topiramate at a dose of 25 mg/day, which than was increased by 25 mg/week until relief was obtained or the maximum tolerated dose was attained. The mean dose of topiramate therapy was 138 ± 85 mg (range: 15–135 mg). Patients kept a headache diary and recorded the frequency and severity of headaches; severity was rated on scale of 1 to 5.

GABA Analog for Painful Diabetic Neuropathy

**Speaker:** Uma Sharma, PhD, Clinical Director for Neuropathic Pain, Pfizer Global Research and Development, Ann Arbor Laboratories, Ann Arbor, Michigan.

Pregabalin 300 mg/day (Pfizer), a structural analog of the neurotransmitter GABA (gamma aminobutyric acid), has been shown to be safe and effective for the treatment of pain associated with diabetic peripheral neuropathy (DPN).

In most patients, DPN is resistant to treatment with simple analgesics and tricyclic antidepressants, anticonvulsants, phe-nothiazines, NSAIDS, and opiates, all of which have been tried with little success. There is, therefore, a need for effective therapy that can relieve the painful symptoms of DPN without risking chemical dependence or affecting glycemic control.

Earlier studies had suggested that pregabalin is effective in relieving pain associated with DPN, so a multicenter (23 centers), double-blind, randomized, parallel-group, fixed-dose, placebo-controlled study was carried out to evaluate the efficacy and safety of pregabalin in DPN. A total of 146 patients with DPN of one to five years’ duration were randomized in this trial, consisting of a one-week baseline phase and an eight-week, double-blind, fixed-dose treatment phase in which the patients were randomly assigned to pregabalin 300 mg/day (76 patients) or placebo (70 patients). The primary efficacy parameter was pain, the score being recorded by the patients in a diary using an 11-point numerical rating scale (0 [no pain] – 10 [worst possible pain]). The primary assessment measure was the endpoint mean pain score (mean of last seven diary entries while on study medication). To be randomized, patients had to have a mean pain score of more than 4 on the daily diary during the baseline phase of the study.

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Compared to placebo-treated patients, pregabalin-treated patients showed significant improvement in the endpoint mean score, with a 1.47 reduction; efficacy was seen at the first time point (week one). In addition, there was a significantly greater proportion of responders (with at least a 50% reduction in pain from baseline to endpoint) in the pregabalin group (40%) compared to the placebo group (14.5%). Supportive evidence also was seen in the significant improvements on pregabalin versus placebo observed for the Short Form McGill Pain Questionnaire, Patient and Clinician Global impression of change, SF-36 Health Survey bodily pain domain, and the Profile of Mood States Tension-Anxiety and Total Mood Disturbance subscales. Of particular importance, there is a durability of the analgesic effect over the eight-week double-blind study phase.

Potassium Channel Blocker for Chronic Motor-Incomplete Spinal Cord Injury

**Speaker:** Daniel Lammertse, MD, Medical Director, Craig Hospital, Englewood, Colorado.

Fampridine-Sustained Release (SR), an investigational specific blocker of fast-activating neuronal potassium channels in demyelinated axons, was well-tolerated and appears to restore neurologic function, showing statistically significant improvement on Subject Global Impression (SGI) and in bowel function in patients with chronic motor-incomplete spinal cord injury.

In an 11-center, double-blind, placebo-controlled, parallel-group study, a total of 91 patients with traumatic spinal cord injury that had occurred 18 months prior to screening, were randomized to receive fampridine-SR (Acorda Therapeutics, Inc.) 25 mg twice daily, fampridine-SR 40 mg twice daily, or placebo for eight weeks (two-week dose escalation, four-week fixed dose, two-week down titration). Efficacy assessments included weekly measures of spasticity (Ashworth Scale of Rigidity, lower extremity tendon reflex, spasm frequency; SGI; and clinical global impression [CGI]), plus baseline and end-of-study measures (International Index of Erectile Function [IIEF], bowel and bladder questionnaires, Functional Independence Measure [FIM]; and Subject Summary Questionnaire [SSQ] at the end of the meeting). Safety was evaluated from adverse event reports and standard clinical assessments.

Overall, 78% of patients completed the study; the incidence of adverse events and patients discontinuing the study was greatest in the fampridine-SR 40-mg-treated patients. Eleven of the 16 patients who withdrew were in the fampridine-SR 40-mg group. Two outcome measures were statistically significant in favor of fampridine-SR 25 mg: SGI, and number of days with bowel movements. Also, in a subgroup analysis, patients with an Ashworth score greater than median at baseline had significantly reduced spasticity on fampridine-SR 25 mg. Several other outcome measures, which did not achieve statistical significance, favored fampridine-SR 25 mg, including the number of bladder accidents per day, and male sexual functioning.