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INSIDE

Resolution of the Prion Debate?

ABSTRACT & COMMENTARY

Synopsis: *The means by which prions cause neuropathologic damage remains to be established.*

Source: Legname G, et al. Synthetic Mammalian Prions. *Science.* 2004:305;673-676.

THE CAUSE OF DISEASES SUCH AS JAKOB-CREUTZFELDT AND MAD cow disease is of great interest. These illnesses were initially designated as slow viral infections. A viral etiology and infective DNA however, has never been established for any of these illnesses. Stanley Prusiner developed a theory that these diseases are caused by conformationally altered proteins, termed prions. It was suggested that the infectious prions, which had an altered conformation, interacted with normal prions in the brain, resulting in conversion of the normal prions to the mutant form. This was particularly the case when the prions developed a beta-pleated sheet structure consistent with amyloid. The prion hypothesis however, has been strongly debated, despite Dr. Prusiner having received the Nobel Prize for this work. The last missing piece of evidence has been to demonstrate that recombinant mouse prion protein can be infectious in mice. In the present study, recombinant mouse prion protein was produced by *Escherichia coli* and then polymerized into amyloid fibrils, that represent a subset of beta pleated sheet-rich structures. The fibrils, containing the recombinant prion, were then inoculated intracerebrally into mice that overexpress normal prions at 16 times the normal levels. The mice were injected with either unseeded or seeded prion proteins. The seeded ones were ones that were induced to take on more amyloid in vitro. The mice developed neurologic dysfunction between 380 and 660 days after inoculation. Brain extracts showed protease-resistant prions by Western blotting. These extracts were then transmitted to wild-type FVB mice and transgenic mice, overexpressing PrP with incubation times of 150 and 90 days, respectively. These mice showed typical neuropathology of prion disorders consisting of vacuolization and gliosis.

COMMENTARY

These experiments appear to be the first to establish that recombinant prions can be infectious in mice. They, therefore, provide the crucial missing link to verify the prion hypothesis. They are not absolute,

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since the initial infectivity was shown in a transgenic mouse overexpressing normal prions. Nevertheless, these experiments are very convincing that prions can indeed transfer infectivity in mice. The means by which prions cause neuropathologic damage, however, remains to be established. — **M. FLINT BEAL**

A New Treatment for Vestibular Neuritis

ABSTRACT & COMMENTARY

Synopsis: *Methylprednisolone significantly improves the recovery of peripheral vestibular function in patients with vestibular neuritis, whereas valacyclovir does not.*

Source: Strupp M, et al. Methylprednisolone, Valacyclovir, or the Combination for Vestibular Neuritis. *N Eng J Med.* 2004;351:354-361.

THE PRESENT PAPER STUDIED THE TREATMENT OF vestibular neuritis. It was assumed, that 1 potential mechanism is reactivation of herpes simplex virus type 1 (HSV-1) infection. If this is indeed the case, corticosteroids, antiviral agents, or a combination of the 2 might prove to be effective in improving the outcome in these patients. This has been shown to be the case with Bell's Palsy. Strupp and colleagues, therefore, performed a prospective, randomized, double-blind, 2-by-2 factorial trial, in which patients with acute vestibular neuritis were randomly assigned to placebo, methylprednisolone, valacyclovir, or the combination of methylprednisolone plus valacyclovir. The vestibular function was determined by caloric irrigation, to determine the degree of vestibular paresis, which was done initially within 3 days after the onset of symptoms and then 12 months afterwards. Strupp et al randomized 141 patients. Thirty-eight received placebo, 35 received methylprednisolone, 33 received valacyclovir, and 35 received the combination of methylprednisolone plus valacyclovir. The methyprednisolone was administered at an initial dose of 100 mg on days 1 through 3, and 80 mg on days 4 through 6, 60 mg on days 7 through 9, 40 mg on days 10 through 12, 20 mg on days 13 through 15, 10 mg on days 16 through 18, and 10 mg on days 20 and 22.

At the onset of symptoms, there was no significant difference amongst the groups in the severity of vestibular paresis. At the 12 month follow-up point, the improvement in peripheral vestibular function was 39.6 ± 28.1 percentage points in the placebo group, 62.4 ± 16.9 percentage points in the methylprednisolone group, 36.0 ± 26.7 percentage points in the valacyclovir group, and 59.2 ± 24.1 percentage points in the methylprednisolone plus valacyclovir group. Analysis of variance showed that methylprednisolone, but not valacyclovir, was effective in improving the patients over the placebo group. The combination of methylprednisolone and valacyclovir was not superior to corticosteroid therapy alone. Strupp et al concluded that methylprednisolone significantly improved the recovery of peripheral vestibular function in patients with vestibular neuritis, whereas, valacyclovir does not.

COMMENTARY

Vestibular neuritis is the second most common cause of peripheral vestibular vertigo, following benign paroxysmal positional vertigo. It accounts for 7% of the patients who present to outpatient clients specializing in the treatment of dizziness. The key signs and symptoms are the acute onset of sustained rotatory vertigo, postural imbalance, with a tendency to fall towards the affected ear with the eyes closed, Romberg's sign, horizontal spontaneous nystagmus towards the unaffected ear, with a rotational component and nausea. Caloric testing of the ear, which is affected, shows ipsilateral hyporesponsiveness or non-responsiveness. The cause of vestibular neuritis is unknown, but could possibly be due to a viral cause. Evidence in favor of this has been circumstantial. HSV-1 DNA has been detect-

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ed on autopsy, with the use of polymerase chain reaction, in about 2 of 3 human vestibular ganglia. This suggests that the vestibular ganglia are latently infected by HSV-1. The recovery from vestibular neuritis is usually incomplete. In view of this, a treatment, which would improve the long-term outcome, is greatly needed. The present report that methylprednisolone is effective, therefore, is of great interest. — **M. FLINT BEAL**

Steroids for Neuromuscular Disease: What's Proven, What's Not?

ABSTRACT & COMMENTARY

Synopsis: *Absence of evidence-based medicine is both humbling, as well as a reminder of how substantial a role the art and oral tradition of medicine plays in the care of neurologic patients.*

Source: Bromberg MB, et al. Corticosteroid Use in the Treatment of Neuromuscular Disorders: Empirical and Evidence-Based Data. *Muscle Nerve.* 2004:30:20-37.

CHRONIC INFLAMMATORY DEMYELINATING POLYRADICULONEUROPATHY: Even prior to its complete clinical explication, steroids were assessed, and found to be beneficial in inflammatory neuropathy. Initially, adrenocorticotrophic hormone (ACTH) was administered. Early reports remain unclear as to whether the patients suffered from acute or chronic polyneuropathy. Eventually, positive responses were associated with administration of ACTH or cortisone in chronic inflammatory demyelinating polyradiculoneuropathy (CIDP). Only 1 randomized placebo-controlled trial of prednisone in CIDP involving 28 patients is reported, claiming a small, but significant, benefit in the treated group. Post hoc analysis of the data found no convincing evidence of benefit. Group studies, however, do support a role for prednisone, with up to 95% of patients doing well at 2 years. Initial dosing and tapering schedules vary between reports, and daily vs alternate-day dosing comparisons are not available. Pulsed high-dose dexamethasone has been tried, reportedly with benefit, but 50% of patients experience side effects including nausea, vomiting, weight-gain, hypertension, and altered mood. Too few patients were studied to recommend dexamethasone.

Myasthenia Gravis: Historically, adrenal and anterior pituitary extracts, implanted desoxycorticosterone pellets, ACTH, and cortisone had all been administered to myasthenic patients with varying degrees of success. In 1966, prednisone emerged as a treatment modality, when mentioned during discussion at a meeting of the New York Academy of Sciences. Both initial daily and alternate-day regimens have since been reported, either as an initial high-dose followed by a taper, or as a low-dose followed by a gradual increase. Early, transient worsening of weakness is known to occur with initiation of treatment. Its pathoetiology remains uncertain, and the alternate-day, low-dose paradigm, with subsequent dose escalation, does not guarantee its prevention. Randomized controlled trials, with prednisone in myasthenia, do not exist, and will never be done, as the collective clinical experience unequivocally supports its long-term efficacy. With up to 17 years follow-up, 80% of patients achieve remission or moderate-to-marked improvement. Controlled, tapering-scheduled trials similarly have never been performed, and hence, medical care is more art than science at this juncture. Slow and steady is the rule, but more than 80% remain on some prednisone, averaging 35 mg on alternate days. Pulsed, high-dose intravenous methylprednisolone, 2000 mg, given q 5 days for up to 3 doses, was beneficial in rapidly reversing myasthenic crisis with respiratory failure in 12 of 15 patients in a single report.

Inflammatory Muscle Disease: Adrenal extract was initially thought to be of questionable benefit in dermatomyositis or polymyositis, but, by the mid-20th century, ACTH and cortisone reportedly, and strikingly, improved both forms of acute myositis. Again, controlled randomized trials of corticosteroids are lacking. Experience attests to a 50% recovery or improvement rate with less aggressive disease, 80% in children, with a 25% mortality rate when myositis is associated with collagen vascular or neoplastic disease. Initiation of therapy usually begins at 1 mg/kg/d for several months, followed by a tapering over 2-5 years, to a maintenance dose of 10-20 mg, required for up to 15 years. Relapse during taper occurs in 40%, and requires increased prednisone dosage followed by a, yet, slower taper. Alternate day therapy, 100 m q.o.d. vs 50 mg q.d., may be equally efficacious with fewer side-effects, but has been reported in few patients.

Duchenne Muscular Dystrophy: Exactly 30 years ago, 14 Duchenne muscular dystrophy patients were given prednisone, and followed for up to 28 months in an open trial. Modest improvement was appreciated. In a second trial, patients treated in a 3-year, alternate-day, randomized, placebo-controlled manner, using prednisolone, showed no significant benefit. Further open-label and randomized trials followed, with some benefit in end-point measures being noted, including muscle strength, forced vital capaci-

ty, and timed, functional tasks. Benefits appeared to stabilize by 3 months, and remained to trial-end in daily, but not alternate-day, dosage-treatment studies. Using historical controls, prolonged treatment (3 years) slowed decline, compared to untreated patients. Weight gain was the most prominent side-effect (average gain, 17%), with 10% developing cataracts and glucosuria in long-term treatment groups. Blinded, placebo-controlled treatment with deflazacort, a weaker steroid with a more advantageous side-effect profile, resulted in improved leg-strength and timed Gowers' maneuver, but time of wheelchair confinement was not different in the treated group.

COMMENTARY

Absence of evidence-based medicine is both humbling, as well as a reminder of how substantial a role the art, and oral tradition, of medicine plays in the care of neurologic patients. Other manner of therapy for 1 or more of the above mentioned neuromuscular disorders, equally experiential and non-evidenced based, include immunosuppression using azathioprine 2-3 mg/kg/d, cyclosporine up to 5 mg/lkg/d, or cyclophosphamide, as intravenous pulse therapy up to 1 gm/m^2 body surface area, or up to 2 mg/kg/d orally (*J Neurol Neurosurg Psychiatry.* 2003;74(Suppl II):ii25-ii31). *Mycophenolate mofetil* (CellCept), 1 gm b.i.d., is gaining increasing popularity, given its ease of use and relatively favorable side-effect profile. Intravenous immunoglobulin has a definite role in several areas, some indications based on rigorous, randomized controlled study. Timing of introduction of these agents remains the subject of debate.

— MICHAEL RUBIN

Pregnancy and Multiple Sclerosis: Predictors of Postpartum-Relapse

ABSTRACTS & COMMENTARY

Synopsis: *These studies provide additional data about the higher risk of relapse, and the greater potential for progression of disability following childbirth.*

Sources: Vukusic S, et al. Pregnancy and Multiple Sclerosis (The PRIMS Study): Clinical Predictors of Post-Partum Relapse. *Brain.* 2004;127:1353-1360; Salemi G, et al. The Relapse Rate of Multiple Sclerosis Changes During Pregnancy: A Cohort Study. *Acta Neurol Scand.* 2004;110:23-26.

VUKUSIC AND COLLEAGUES PROSPECTIVELY STUDIED 227 patients who had multiple sclerosis (MS) for at least 1 year, and then had a full-term delivery. They reported a 2 year postpartum follow-up. Compared with the pre-pregnancy year, there was a reduction in the annualized relapse rate during pregnancy, most apparent in the third trimester (0.7 down to 0.2). This was followed by a marked increase in the first 3 months after delivery,[1,2] and gradually returning to the pre-pregnancy rate over 9 to 12 months. A postpartum attack, in the first 3 months, was experienced by 28% of patients. Also of concern, the mean confirmed disability score of the total population progressed significantly from 1.3 pre-pregnancy, to 1.6 in the first 3 months postpartum, but then continued to increase to 1.8 at year 1, and 2.0 at year 2. There were 3 clinical variables that correlated with the occurrence of a postpartum attack: An increased relapse rate in the pre-pregnancy year, an increased relapse rate during pregnancy, and a higher disability score at pregnancy onset. Neither breast-feeding nor epidural anesthesia had an effect on relapses and disability.

In a second study by Salemi and colleagues, the investigators examined the mean yearly relapse-rate in 70 MS patients, for a total of 98 pregnancies. They confirmed that the mean annual relapse rate of 0.72, decreased significantly to 0.48 in the third trimester, and then increased to 0.84 in the puerperium period. The calculated relative risk of relapse was 0.63 during pregnancy, rebounding to 1.36 during puerperium.

COMMENTARY

MS is a neurological disorder predominantly affecting young women of child-bearing age. There are recognized environmental determinants for disease pathogenesis, including complex hormonal effects on the immune system, which are poorly understood. For example, prior studies have shown a higher incidence of relapse and gadolinium-enhancing activity on brain MRI in women during their menstrual period. This may result from the drop in estrogen, which then leads to an increase in pro-inflammatory cytokines (such as IL-1 and IL-2) and T-cell activation. Similar hormonal effects may be related to postpartum flares of disease. During pregnancy, there may also be placental secretion of cytokines such as IL-10 and alpha-fetoprotein, that may downregulate the immune response. Autoimmune disorders, such as MS and rheumatoid arthritis, are ameliorated during pregnancy, but often worsen in the postpartum period. Many patients will have their initial presentation of disease during this vulnerable phase, although no clear statistics exist for patients who are diagnosed in puerperium.

The above studies provide additional data about the higher risk of relapse, and the greater potential for progression of disability following childbirth. The study by Vukusic et al provides helpful 2-year follow-up data, which details the significant worsening of disease postpartum. Physicians

should counsel their patients that they may have increased symptoms following delivery, and additional support may desirable in caring for their newborn. Further, patients may need to interrupt breastfeeding for urgent drug intervention with MS relapses. Clinicians may choose to identify those patients at higher risk for relapse and disease progression, and treat aggressively with immuno-modulatory agents prior to the obvious onset of postpartum symptoms.
— **BRIAN R. APATOFF**

Antiplatelet Therapy for Secondary Stroke Prevention: MATCH Trial Results

ABSTRACT & COMMENTARY

Synopsis: *The MATCH data provide quite strong evidence that the clopidogrel-aspirin combination is a less favorable option than previously thought, but its use may not be completely contraindicated.*

Source: Diener HC, et al. Aspirin and Clopidogrel Compared with Clopidogrel Alone After Recent Ischaemic Stroke or Transient Ischaemic Attack in High-Risk Patients (MATCH): Randomized, Double-Blind, Placebo-Controlled Trial. *Lancet.* 2004;364:331-337.

Aspirin is the mainstay of treatment for secondary stroke prevention, but controversy remains regarding its optimal dosing and possible combination with other agents. Recent publicity regarding patients who may be aspirin resistant has further clouded the issue. Clopidogrel (Plavix) is a thienopyridine derivate that works differently than aspirin, inhibiting platelets by blocking the adenosine diphosphate (ADP) receptor. It has come into wide use as a replacement for the agent ticlopidine (Ticlid), which had multiple side effects, including the induction of thrombotic thrombocytopenic purpura (TTP). Clopidogrel has been shown to have an 8.7% relative benefit over aspirin in the prevention of vascular events (CAPRIE study), and has been shown to be beneficial in combination with aspirin in patients with unstable angina (CURE trial). In practice, the CURE data have been extrapolated to stroke/TIA patients, but the safety and efficacy of this regimen has never been systematically studied.

The MATCH trial, reported in *Lancet* this month, randomized approximately 8000 patients who had suffered a recent stroke/TIA, to either clopidogrel (75 mg) alone, or in combination with aspirin (75 mg). Patients in the study were considered high risk, since each was required to have had a prior stroke, myocardial infarction (MI), diabetes, or symptomatic peripheral arterial disease. The primary endpoint of MI, ischemic stroke or vascular death, occurred in 16.7% of the clopidogrel arm, and in 15.7% who received the combination. This absolute difference of 1%, and relative difference of 6.4%, was not statistically significant. Subgroup analysis comparing patients presenting with stroke vs TIA, or those with risk factors such as diabetes or prior MI, also did not show any significant differences. There was, however, a significant increase in life-threatening bleeding in patients on combination therapy (2.6% compared with 1.3% on clopidogrel alone, $P < 0.001$). Intracranial hemorrhage was also more common among patients on the combination ($P = 0.029$). Despite this, there were no reports of hemorrhagic transformations of ischemic stroke, and although bleeding was considered life-threatening, it did not translate into an increased mortality rate.

COMMENTARY

The MATCH data provide quite strong evidence that the clopidogrel-aspirin combination is a less favorable option than previously thought, but its use may not be completely contraindicated. Recurrent stroke/TIA is known to occur within days after an incident event, and MATCH recruited patients up to 3 months following their qualifying event. Among MATCH patients recruited within 1 week post-stroke, there was actually a 15.6% event rate on combination therapy vs 18.7% on clopidogrel alone, a difference of 3%, which is triple that of the overall cohort. It remains possible that combination therapy, perhaps even including a loading dose of clopidogrel (300 mg was used in the CURE trial), might provide additional benefit post-stroke, if the earliest days to weeks could be properly studied.

Data from other studies will be available in the coming years. The PRoFESS trial will be comparing clopidogrel to a combination of aspirin and extended release dipyridamole (Aggrenox), with or without the angiotensin receptor blocker telmisartan (Micardis). Interestingly, the PRoFESS trial previously included aspirin in the clopidogrel arm, but removed this on the basis of the MATCH results. PRoFESS will provide the head-to-head comparison between Plavix and Aggrenox that we sorely need. Until then, these unfortunately expensive agents can be used interchangeably, and provide limited, but tangible benefit over aspirin alone.
— **ALAN Z. SEGAL**

Melatonin is Effective for Sleep Disorders in Young People with Developmental Delays, but has Variable Effects on Seizures

ABSTRACT & COMMENTARY

Synopsis: *It seems prudent to strongly consider use of melatonin in our cognitively delayed patients with disordered sleep, but to monitor those with epilepsy very closely for exacerbation, and withdraw the drug.*

Source: Coppola G, et al. Melatonin in Wake-Sleep Disorders in Children, Adolescents and Young Adults with Mental Retardation with or without Epilepsy: A Double-Blind, Cross-Over, Placebo-Controlled Trial. *Brain Dev*. 2004;26:373-376.

SLEEP PROBLEMS ARE AMONG THE MOST COMMON, recurrent complaints brought to neurologists, by caretakers of those with cognitive delays. Poor sleep is a significant family stressor, produces increased daytime somnolence, behavioral problems, school/work difficulties, and frequently exacerbates epilepsy. The prevalence of sleep difficulties, in intellectually impaired populations, has been found to range from 15%-67%.

This paper presents a small randomized, double-blind, cross-over, placebo-controlled trial of melatonin in mentally retarded young people with sleep disturbances. Initial screening was by questionnaire regarding sleep latency, awakenings, total sleep time by day and night, and early arousals. Thirty-two patients were enrolled. Patients had cognitive impairment from mild to severe, a broad range of seizure types (18/25 were epileptic), as well as a variety of related pathologies, including genetic syndromes (20%), cerebral palsy (32%), and congenital visual impairment (16%).

Caregivers kept sleep logs during constant nocturnal patient observation. Polysomnograms were performed when seizures were suspected to be causing, or mimicking, a sleep abnormality. Seizure diaries were also kept, with frequency, type, and duration, before and during the trial. No changes were made to any antiepileptic drugs (AEDs).

Patients were randomized to either oral synthetic fast-release melatonin (3 mg q.h.s., increasing 3 mg weekly as tolerated, if needed, to 12 mg q.h.s. max) or placebo for 4 weeks, underwent a 1 week cross-over, then a second 4 week phase. 25/32 patients completed both phases (16 male; 9 female; aged 3.6-26 years). Responders then entered a 2-month, open-label phase.

Melatonin had a significant effect on sleep latency (P = 0.019) at doses of 3 mg/d (29.2%), 6 mg/d (45.8%), 9 mg (20.8%), and 12 mg (4.2%; 1 patient). One patient did not respond. No effect on nocturnal awakenings (P = 0.768) or daytime sleep (P = 1) was found. Interestingly, total nocturnal sleep time increased with either melatonin or placebo vs baseline (7.9, 7, and 4.4 h respectively), though Coppola and colleagues state that the data are skewed by persistence of melatonin effect into the placebo phase, in those randomized first to melatonin. There was a trend toward fewer early arousals (P=0.123), with melatonin as well. Improved behavior and daytime alertness was noted (though not quantified) in half of the treated individuals, and families reported subjective improvement in overall quality of life. No side-effects were reported by any participants, including the 7 drop-outs.

Of note, 2 of 11 previously seizure-free epilepsy patients, relapsed after 1 month, and remitted after discontinuing melatonin.

Of the 7 patients whose epilepsy was uncontrolled from the start, 1 became seizure-free, 2 improved, 2 worsened, and 2 were unchanged.

Further improvements in sleep latency (mean, 0.2 h), duration of night sleep (mean, 8.4 h), and early arousal (mean, 2.0) were seen in the final 2 month, open-label phase of the study.

COMMENTARY

Melatonin, a.k.a. N-acetyl-5-methoxytryptamine, is synthesized from serotonin in the pineal gland. It is regulated by the light-dark cycle, and plays a role in immunity, endocrine regulation, the stress response, as an antioxidant, and in the regulation of circadian rhythms.

Given melatonin's well-known ability to reset the sleep cycle, and induce and improve sleep, one would expect that epileptics might experience decreased seizure frequency from melatonin treatment, via a reduction in sleep deprivation alone. Additionally, abundant data, in a vast array of animal seizure models, demonstrate a direct anticonvulsant effect. In humans, reduced melatonin levels have been found in patients with intractable epilepsy, as well as in non-epileptics with mental retardation. Lastly, several small studies have shown clinical improvement in epileptic children who took melatonin. On the other hand, there have been occasional reports of melatonin having proconvulsant effects.

In the study summarized here, however, there was no reliable effect of melatonin on epilepsy, despite a clear improvement in sleep latency, and a likely improvement in total sleep and fewer arousals. The effects seen here on sleep and behavior, similar to those seen in a number of other small studies of melatonin in children with cognitive disabilities, imply that there is clear utility of melatonin for sleep disturbance in

mentally disabled populations. However, several studies, including this one, imply that despite the experimental evidence suggesting that melatonin has inherent anticonvulsant properties, it may exacerbate seizures in some children and young people with epilepsy, while helping many others.

Given melatonin's obvious benefit to many, but a significant possible risk to some epileptics, we eagerly await a larger, prospective, double-blind, placebo-controlled study with sufficient power to allow for multivariate analysis by seizure type, sex, age, mental and/or visual disability, specific concomitant AED use, and other factors. Only then, might we determine whether there are definable subgroups that might particularly benefit from melatonin therapy, or others in whom it might be a relatively contraindicated. Until then, it seems prudent to strongly consider use of melatonin in our cognitively delayed patients with disordered sleep, but to monitor those with epilepsy very closely for exacerbation, and withdraw the drug. — **SUSAN E. SNYDER**

Highlights of the 9th ICADRD Meeting

ABSTRACTS & COMMENTARY

Synopsis: *The hundreds of presentations at this meeting provided encouraging evidence that existing Alzheimer's therapies may have greater benefits than first realized, and that a new generation of potential disease-modifying therapies for AD may be on the way.*

Sources: Petersen R, et al. "Donepezil and Vitamin E as Treatments for Mild Cognitive Impairment" 9th ICADRD Presentation Number: O1-05-05; Pomara N, et al. "Memantine Monotherapy is Effective and Safe for the Treatment of Mild to Moderate Alzheimer's Disease: A Randomized Controlled Trial, 9th ICADRD, presentation O1-05-04; Aisen PA, et al. Clinical Data On Alzhemed™ After 12 Months Of Treatment In Patients With Mild To Moderate Alzheimer's Disease. 9th ICADRD Presentation Number: O1-05-06; Gilman S, et al. Neuropsychological, CSF, and Neuropathological Effects of A-Beta Immunotherapy (AN1792) of Alzheimer's Disease in an Interrupted Trial, 9th ICADRD Presentation O4-05-07; Fox N, et al. Effects of A-Beta Immunotherapy (AN1792) on MRI Measures of Brain, Ventricle and Hippocampal Volumes in Alzheimer's Disease. 9th ICADRD Presentation O4-05-08.

THE 9TH INTERNATIONAL CONGRESS ON ALZHEIMER'S Disease and Associated Disorders (ICADRD), held in Philadelphia during July 2004, was attended by several thousand Alzheimer's researchers and clinicians from around the world. The hundreds of presentations at this meeting provided encouraging evidence that existing Alzheimer's therapies may have greater benefits than first realized, and that a new generation of potential disease-modifying therapies for AD may be on the way.

This was the first ICADRD meeting in which the results of MCI prevention trials were available. Dr. Ronald Petersen presented the results of a large-scale AD prevention study that compared the effect of 2000 IU/day of vitamin E, 10 mg/d of donepezil, or placebo on progression from Mild Cognitive Impairment (MCI) to AD. This 3-year trial involved 769 patients with amnestic MCI from 69 centers in the United States and Canada. Petersen and colleagues documented progression from MCI to possible or probable AD in over 200 cases, representing a cumulative conversion rate of 13% per year. No significant differences were observed in rate of development of AD in vitamin E, donepezil, and placebo-treated patients at the 3-year study endpoint. However, donepezil-treated patients showed a significant delay in the progression to AD over the first 18 months of the study, equivalent to approximately 6 months difference relative to placebo. While these findings could be interpreted as evidence of a purely symptomatic effect of donepezil in MCI, it is noteworthy that 4 other agents (vioxx, celebrex, vitamin E, and galanthamine) have been studied in similar large-scale MCI trials. Thus far, only donepezil has been reported to significantly decrease conversions from MCI to AD over an 18-month period.

Memantine, an NMDA-receptor antagonist, is currently approved in the United States for treatment of moderate-to-severe AD, but not for treating mild cases. Dr. Nunzio Pomera presented results of a 24-week, double-blind, placebo-controlled trial testing the safety and efficacy of memantine in mild to moderate AD. A total of 403 patients enrolled, and 82% completed the trial. Patients treated with 10 mg b.i.d. of memantine, declined less over 24 weeks than placebo-treated patients on the ADAS-cog ($P = 0.003$) and the CIBIC+ ($P = 0.004$). At this dosage, memantine was found to be safe and well-tolerated. The effect of memenatine monotherapy in mild AD patients was not compared to that of the already-approved cholinesterase inhibitors. However, memantine's mechanism of action is different from the cholinesterase inhibitors, which could lead to its approval for mild AD, even if it is found not to have equal efficacy.

Several agents that target amyloid production, fibrillogenesis, and clearance were discussed at the ICADRD. Dr. Paul Aisen reported results from a 21-month open-label extension of a double-blind, Phase 2 AD treatment trial of the Alzhemed, a small molecule that is reported to function as an amyloid fibrillogenesis inhibitor. Results from a 3-month double-blind period indicated that the drug was safe and well-tolerated at all doses, with only mild dose-related side effects. Results of tests of cognitive function (MMSE and ADAS-Cog) in the first 3 months were not significantly different in Alzhemed-treated patients than those who received placebo. In 14 patients followed up to 21 months, possible benefits were reported relative to extrapolated controls. Dr. Aisen reported that a large scale, 18-month Phase III trial of Alzhemed is now being initiated.

Among the most interesting series of presentations at the 9th ICADRD, were those in follow-up to the Elan/Wyeth's Phase IIa AN-1792 immunotherapy trial, which was discontinued in 2002, owing to the development of meningoencephalitis in 18 (6%) of 300 immunized AD patients. Dr. Sid Gilman presented neuropsychological and laboratory test results from this trial. The primary cognitive outcome measures (including the MMSE, ADAS-Cog, and CDR) were not significantly different in immunization responders than placebo-treated patients, although a possible difference in delayed verbal memory was observed favoring responders. Concentrations of tau protein in cerebrospinal fluid were relatively reduced in responders, suggesting possible improvement. However, CSF Aβ-42 levels were not significantly different at month 12 between responders and matched placebo treated patients. Dr. James Nicoll presented results from autopsy studies of 4 patients who died several months after receiving their last injection in AN-1792 trials. Substantial reduction in amyloid burden, and evidence of amyloid clearance, was observed in 3 of the 4 autopsies. These neuropathological studies provide some of the strongest evidence, to date, that immunotherapy can reverse amyloid-related pathology in actual patients with AD. Dr. Nick Fox reported on changes in brain volume over the 12 months after immunization, based on quantitative volumetric MRI studies. Much to everyone's surprise, there was a significantly greater amount of volume reduction observed over 1 year in the whole brain of those who were treated and responded to immunization, compared to those who went untreated. A greater increase in ventricular volume was also observed in successfully immunized patients. Dr. Fox suggested that this increased rate of shrinkage of the brain could be the result of removal of beta-amyloid, which occupies a substantial volume of the brain in AD. An alternative explanation not discussed is that the ventricular volume increased disproportionate to parenchymal shrinkage, as a result of a mild reactive hydrocephalus, which can result from subclinical meningoencephalitic inflammation, brought about by immunization. Further studies of the AN-1792 preparation are not planned, however, Elan has begun a Phase 1 trial of an anti-amyloid monoclonal antibody involving a passive immunization strategy. — **NORMAN RELKIN**

CME Questions

9. Which of the following agents is a small molecule inhibitor of beta amyloid fibrillogeneis?
- a. Donepezil
- b. Rivastigmine
- c. Alzhemied
- d. AN-1792

10. Which of the following is based on uncontested, double-blind placebo-controlled studies:
- a. prednisone in chronic inflammatory demyelinating polyradiculoneuropathy
- b. prednisone in myasthenia gravis
- c. prednisone in polymyositis
- d. prednisone in dermatomyositis
- e. none of the above

11. The highest relapse rate in multiple sclerosis patients occurs
- a. during the first 3 months post-partum.
- b. during the first trimester of pregnancy.
- c. during the last trimester of pregnancy.
- d. at the time of conception.

Answers: 9. (c); 10. (e); 11. (a)

Readers are Invited. . .

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