

Medical Update Memo

October 15, 2009

Therapeutic Strategies for MS and More Highlighted at ECTRIMS Conference

Summary

Hundreds of multiple sclerosis clinicians and investigators convened to present findings and develop collaborations at one of the top MS-focused conferences in the world. The 25th Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) was held September 9-12, 2009, in Dusseldorf, Germany. Here is just a sample of these presentations, full details of which are available online at <http://www.akm.ch/ectrims2009/>.

Details

Latest on Oral Drugs in the Pipeline

As several oral treatments wrap up phase III studies and prepare to submit data to the FDA, investigators reported on additional safety and effectiveness data from phase II and III studies:

- Dr. Mark Freedman and colleagues reported on phase II results of a study in which two doses of oral teriflunomide (sanofi-aventis), an immune modulator, or placebo, were added to ongoing interferon beta-1a therapy in 116 people with RR MS. Disease activity as observed on MRI scans was reduced by 56% over placebo in the lower dose group, and by 81% over placebo in the higher dose group. Phase III studies of teriflunomide are underway in relapsing MS and in people at high risk for developing MS. (#P878)
- Dr. Gavin Giovannoni and colleagues analyzed data from the CLARITY study, a phase III trial of oral cladribine (EMD Serono). Cladribine – a drug that interferes with the immune cells that underlie the attack in MS – as reported previously reduced the relapse rate significantly more than inactive placebo in 1,326 people with relapsing-remitting MS (RR MS). Now the team reports that treatment with cladribine resulted in a greater proportion of people with no new disease activity (44.3% on a higher dose, 43% on a lower dose) than inactive placebo (16%). The company plans to submit to the FDA for approval of cladribine to treat MS in 2009. (#P471)

- Dr. Frederik Barkhof and colleagues presented MRI findings from the TRANSFORMS study that compared two different doses of oral fingolimod (FTY720) with Avonex® (interferon beta-1a, Biogen Idec) over a one year period. Previous results reported significant reductions in relapse rates with the study treatment; now the team reports as that fingolimod reduced active areas of tissue damage observed on imaging scans. Phase III studies are ongoing. (#89)
- Dr. Giancarlo Comi and colleagues reported on a long-term extension of the phase II study of laquinimod (Teva Pharmaceutical Industries), an oral immune modulator now in phase III trials. Laquinimod reduced disease activity by 40.4% compared with placebo in a study of 306 people with RR MS treated for 18 months; 155 of 209 patients who entered the extension have been treated for an additional 24 months. The “annualized” relapse rate for this group is 0.46, compared with 0.53 in the original study; 10.5% of participants have shown progression on the EDSS disability scale, compared with 14.8% during the first 18 months; and 61% have not had new active areas of tissue damage on MRI scans. The most common side effects include nasopharyngitis (25.8%), back pain (12.4%), and headache (8.1%). (#P443)

Some Success, Some Failures in Novel Strategies

ECTRIMS featured mixed results on novel therapeutic strategies:

- One experimental strategy under study for treating MS is cell transplants, such as “mesenchymal stem cells,” which are derived from bone marrow. Dr. Mark Freedman and colleagues reported on the formation of the International Mesenchymal Stem Cell Therapy Study Group. This group – which includes many of the world’s experts in this type of cell therapy – met in 2009 to develop a protocol for propelling this research forward. They formed a consensus on numerous issues related to study design, and have agreed to begin studying this strategy in active forms of MS, including RR MS, secondary-progressive MS with ongoing relapses or primary-progressive MS with disease activity on MRI scans. (#49)
- Dr. Frederik Barkhof and colleagues administered the immunosuppressive drug temsirolimus or placebo to 297 people with RR MS for nine months. Temsirolimus reduced the rate of brain tissue volume loss significantly more than placebo, as measured by two separate methods. The results suggest that this drug may protect nerve tissue from damage in MS, as well as suppress the immune attack. (#P481)
- Dr. Raj Kapoor and colleagues reported on a study of the epilepsy (and potentially neuroprotective) drug lamotrigine in 120 people with secondary-progressive MS. The primary goal of the study was to determine the treatment’s effect on brain tissue volume loss; the results show tissue loss increased, in fact, although losses were recovered when treatment was stopped. Surprisingly, participants taking lamotrigine improved in walking speed, although the study was not designed specifically to measure this as a primary outcome. (#135)

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- Dr. Emanuelle Waubant and colleagues reported on a study of atorvastatin and interferon beta or placebo in 81 people with Clinically Isolated Syndrome (CIS, a single, isolated neurologic event suggesting loss of nerve-insulating myelin). Previous studies have suggested that cholesterol-lowering “statins” can alter immune responses in a way that may hold promise in treating MS. The study was designed for 152 people, but enrollment stalled at 81, and thus it was not possible to detect if the primary endpoints – to decrease or delay clinical and MRI disease activity – were reached. However, the proportion of people who did not develop new tissue damage up to month 12 was 55.3% in the atorvastatin group and 27.6% in the placebo group, indicating a trend toward effectiveness. (#132)

Tysabri® and PML

There continues to be considerable interest in determining how to lessen the risk of PML (progressive multifocal leukoencephalopathy, a viral infection of the brain that usually leads to death or severe disability) in people treated with Tysabri® (natalizumab, Biogen Idec and Elan Pharmaceuticals).

- Dr. Richard Rudick and colleagues (Poster 883) found, in a large group of people tested before and after initiating therapy, that the frequency of detection of JC virus (the virus that causes PML) in blood or urine in those treated with Tysabri over 48 weeks was no different from that seen in healthy controls. This suggests that these tests are not helpful in screening people on treatment for risk of PML.
- Another approach under discussion has been to consider instituting a “drug holiday” at some point after being on Tysabri therapy. However, data presented by Dr. Paul O’Connor and colleagues indicated that MS disease activity rapidly begins to return after cessation of Tysabri, whether or not another disease modifying agent is being used (Poster 793).

Improving MS Symptoms

Several teams addressed the variety of symptoms experienced by people with MS:

- Dr. Z. Ambler and colleagues reported on a study of an oral spray drug derived from whole cannabis plants (Sativex® -- GW Pharmaceuticals, Salisbury, UK) in 572 people with all types of MS. Of this group, a four-week preliminary study targeted 241 as “responders” who then enrolled in a 12-week study in which the drug was compared with placebo. In this second phase, Sativex significantly improved spasticity compared with placebo. In the first phase, the most common adverse effect was dizziness (14% of those taking Sativex), and in the second phase, urinary tract infection (7% of the Sativex group). (#P844)

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- Dr. John Zajicek reported results from the MUSEC study, which evaluated oral cannabis extract for treating muscle stiffness in 400 people with all types of MS. In this study, muscle stiffness improved by almost twofold in the group taking cannabis extract compared to placebo, and improvements were also noted in body pain, spasms and sleep quality. The most frequent adverse events were urinary tract infections, dizziness, dry mouth, and headache. (#881)
- Dr. N. Sharafaddinzadeh and colleagues administered low dose naltrexone (an opioid antagonist used to treat addictions to opioids and alcohol) or placebo to 50 people with MS to determine its effect on quality of life. Using a scale that measures physical and mental aspects of health status (MSQLI), the group found no significant difference between the naltrexone and placebo groups. (#P865) Read more about naltrexone research in MS.
- Dr. Charles Bombardier and colleagues used counselling to improve the participation of 102 people with MS and major depression in an exercise program. One face-to-face and five telephone sessions were conducted to promote motivation and commitment to the program. After 12 weeks, the group receiving the counselling showed significant improvements on several scales including those rating depression and fatigue, compared with a group not receiving the counselling. Those who improved also showed benefits in pain symptoms and community integration. (#P841).

Exploring the Underpinnings of MS

ECTRIMS featured some novel insights into the development of MS:

- Among many presentations focusing on genes that make people susceptible to developing MS and that may dictate its variability among people, Dr. M. Vellinga and colleagues reported on a study of focused on determining whether genetic variations could explain differences in the location of MRI-detected brain lesions in 208 people with MS. They found three gene variations that were associated with tissue damage located near the ventricular system of the brain (a set of structures containing cerebrospinal fluid). These gene variations occurred in the MHC or “major histocompatibility complex,” which helps determine immune responses and has shown definite links MS. Further research along these lines may provide valuable insight into why MS can be so different among individuals. (#p258)
- In the annual Charcot Award Lecture, Dr. John Prineas reviewed what has been learned in recent studies of MS pathology, and offered predictions for the next major insight in MS research. He discussed the fact that in a related disease, neuromyelitis optica (NMO), the aquaporin 4 antibody used to help diagnose NMO was recently discovered to be targeting astrocytes, star-shaped cells that support brain structure and function and which are known to be involved in creating scar tissue in MS. Dr. Prineas showed evidence of astrocytic involvement and reduced aquaporin 4 levels in tissue from people with MS, and suggested these cells may play a major role in MS damage. (#79, p585)

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With information from the National MS Society (USA)

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