



Highlights from the 2017 AAN Annual Meeting

The American Academy of Neurology (AAN) annual meeting is one of the top conferences for people who study and treat MS. ACP representatives have attended this meeting annually since 2003. Since this year's meeting was in our backyard (Boston), several of us took the opportunity to attend, joining over 10,000 neurology professionals from across the world.



The MS-related presentations and classes spanned a variety of topics, from pregnancy in MS, to new imaging techniques, to diagnosis, and so on. Below are summaries of the presentations we found particularly interesting, mostly on the topics of MS medications (disease-modifying therapies) and risk factors for MS. If you'd like to learn more or explore other topics, the meeting abstracts are available for everyone to browse. Just go to this link – <http://submissions.mirasmart.com/AAN2017/itinerary/SearchHome.asp> – and search for the topics that interest you.

Disease-modifying therapies (DMTs):

Ludwig Kappos reviewed the positive results of the Phase III study of Novartis's oral drug siponimod in SPMS, which were first presented atECTRIMS last fall. Siponimod is a similar compound to fingolimod (Gilenya®). The conclusion is that siponimod works to decrease disease progression and looks promising as a treatment for SPMS.

Another set of results were presented by Peter Calabresi on a Phase II study of opicinumab. This Biogen drug blocks a factor (LINGO-1) that interferes with remyelination. Four doses were tested in people with relapsing-remitting or secondary progressive MS who were simultaneously treated with interferon-beta (Avonex®). Interestingly, the people on the two middle doses had better outcomes than those on the highest or lowest doses. The outcomes seen in the study fell short of what was hoped for. However, Biogen saw enough signs of promise to continue, and will use what they learned about people who did well on the drug to design future studies of opicinumab.

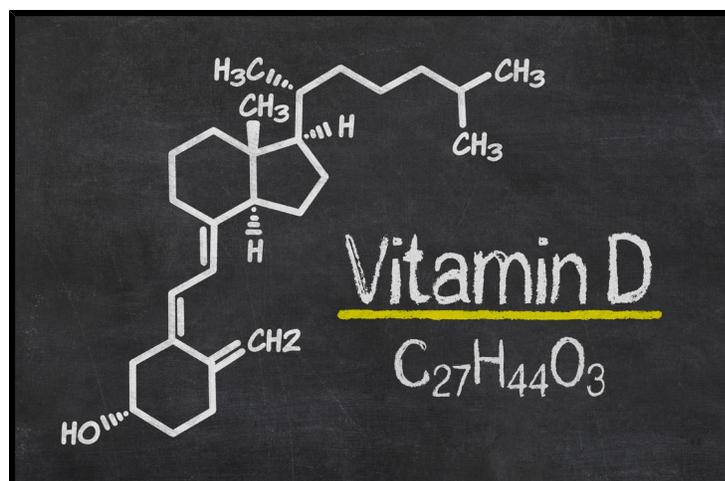
One of the panels featured drugs that were very early in the development process. David Weinstein reviewed data from a study of CHS-131, a drug that is similar to the diabetes medicine pioglitazone but tweaked to have fewer side effects. A small study in MS showed a reduction of inflammatory lesions and brain atrophy (shrinkage) compared with placebo. No safety problems were detected, so the company developing CHS-131 (Coherus) is proceeding with further study of a higher dose. Also, a research program at the University of California San Francisco that screens drugs for their remyelination potential found that the drug bazedoxifene shows promise. This drug is a selective estrogen receptor modulator under development for postmenopausal osteoporosis.

While many presentations describe treatments that are not yet on the market, there is still much to be learned about the long-term performance of available DMTs. Douglas Arnold provided results from people who enrolled in the CARE-MS I alemtuzumab study. These participants received alemtuzumab upon joining the study and 12 months later, and have since been followed for 6 years. Over the follow-up period, 66% had no new or enlarged MRI lesions, and 63% needed no further treatment.

One of the main conference sessions, called “Controversies in Neurology,” included a debate about whether DMTs should be discontinued in people with progressive MS. John Corboy argued in favor of stopping DMTs upon evidence of progression. He stated that in clinical trials with people with MS whose age is < 40 years, the DMTs have demonstrated a benefit on a variety of standard outcome measures. However, for those above 40 years old, the DMTs have not demonstrated benefit on standard outcome measures. He proposed discontinuation and medical monitoring. Robert Naismith, taking the other side of the argument, conceded some of Dr. Corboy’s points but said that there were still opportunities for people with progressive MS to derive benefit from treatment with DMTs. For example, certain clinical trials have shown benefits for upper extremity function, cognition and vision. He focused also on “What does the patient want?” It was concluded that a formal study was needed.

Risk factors:

Vitamin D deficiency has been associated with a higher risk of developing MS, which begs the question of whether vitamin D supplementation can help reduce disease activity in people already diagnosed with MS. William Camu and Joost Smolders described two similar European studies comparing the combination of interferon beta (Rebif®) with vitamin D3 to interferon beta alone in people with MS. The studies showed some reductions in relapses and MRI activity among people taking vitamin D. However, most of these results were not statistically significant, likely due to the small numbers of participants



and high percentage of dropouts. For instance, in Dr. Camu's study, 24% of the placebo recipients stopped taking Rebif partway through the study due to relapses, so they could not participate for the full 2 years.

Another set of presentations dealt with the topic of viral infections as risk factors for MS. Annette Langer-Gould presented data from a Southern California population showing some differences in antibodies to Epstein Barr virus (EBV) and cytomegalovirus (CMV) in Caucasians, African-Americans and Hispanics. A similar study of patients at 16 MS pediatric centers found a strong association between MS and past EBV infection in all racial and ethnic groups. In this study, the MS patients had higher vitamin D levels than controls, probably because children with MS are more likely to receive vitamin D supplements than other kids.

Noriko Isobe reviewed what we know to date about the genetics of MS and to assess whether genetic data could someday be used to guide MS healthcare. So far over 230 gene variants have been found to affect the risk of MS. Dr. Isobe and colleagues determined the "genetic burden" of people with MS and controls by seeing how many of these MS risk variants they have. They found that men have a higher genetic burden than women; that having more variants in a specific region with immune-related genes was associated with younger age of onset and brain atrophy in women with RRMS; and that people with a single MS symptom tend to have additional disease activity faster if their genetic burden is high.

Sunali Goonesekera gave a presentation on the worldwide prevalence of MS. Estimates range from less than 1 in 10,000 in Africa and the Middle East to more than 1.3 in 1,000 in Europe and North America. Substantial increases in prevalence are predicted in Asian, Middle East and Africa, in part because of improvements in diagnosis. RRMS is the most common type of MS worldwide, and there is little variation in the distribution of subtypes despite differences in prevalence.

Finally, Michael Levy described the discovery of a rare genetic variant (VPS37A) and its association with a familial form of transverse myelitis. He and his team identified the gene variant in 2 sisters, one who developed TM at age 15 and the other who developed symptoms at age 50. The Hopkins group then used ACP Repository biosamples to find one new familial TM patient with the same gene variant. The gene codes for a protein involved in a cellular recycling system that is associated with other neurodegenerative diseases.

Comparative effectiveness:

Perhaps the biggest puzzle facing neurologists and people with MS today is determining which MS drug will work the best for a given person. To partially solve this puzzle, a number of "comparative effectiveness" studies have been conducted or are underway which compare two or three drugs on a set of outcomes.

One of the poster sessions featured these types of studies. We've summarized a few of the research topics to show the type of research being done in this area and the range of outcomes being evaluated:

- Fingolimod (Gilenya®) and interferon beta-1a (Avonex®) compared on a blood biomarker (neurofilament light chain)
- Fingolimod and glatiramer acetate (Copaxone®) compared on brain volume changes
- Dimethyl fumarate (Tecfidera®), fingolimod and teriflunomide (Aubagio®) compared on risk of relapse
- Peginterferon beta-1a (Plegridy®) and teriflunomide compared on disability worsening and relapse rate
- Fingolimod, interferons, and glatiramer acetate compared on treatment satisfaction

While these comparisons are interesting, they can't tell an individual person with MS which of the treatments being compared would be better for them based on their own individual characteristics and preferences. ACP is working on a "personalized medicine" approach to generate that type of evidence. We hope to be able to present findings from this work at an upcoming AAN conference!

Overall impressions:

25 years ago, neurologists had very few "tools" to treat neurological disorders: epilepsy drugs, drugs for Parkinsons symptoms, some migraine and pain drugs, and a few others. Now there are medications for some of the formerly untreatable neurological conditions, with multiple MS DMTs leading the way. New treatments for spinal muscular atrophy and advances in stroke treatment provide brighter outlooks for the very young and not-so-young alike.

The past 25 years have seen a transformation of neurology from the old adage "Diagnose and Adios." The coming years promise a lot for people with neurological conditions and brain injury. We look forward to continuing to move the MS field forward with our colleagues from around the world.