HDSA Convention Notes: Potential New Therapies

This session was moderated by Dr. **Steven Finkbeiner**. The first speakers were Dr. **Joachim Tedroff**, chief medical officer, and **Asa Rembrandt**, project manager for **ACR-16.** The dopamine stabilizer ACR-16 now has a generic name pridopidine and a trade name of **Huntexil**. There are ten studies ongoing or planned for this drug.

The first Phase III study, called Mermai-HD, ended this winter. It was conducted at 32 centers in eight European countries. The end point for this trial was the Modified Motor Score (MMS) of the United Huntington's Disease Rating Scale (UHDRS), a subset of the Total Motor Score (TMS) of the scale. Two dosages were tried, 45 mg and 90 mg.

Statistical significance was not achieved on the primary endpoint although there were promising results. Statistical significance is determined through a mathematical formula that takes into account the size of the difference between the experimental group and the control group, the number of people in the trial, and the amount of individual variation within each group. The formula will tell us how likely it is that the differences are just a result of random chance and not a result of a real treatment. The lower the probability statistic the better.

The probability statistic for differences between the experimental groups and the control group was .042. Had there been only the 90 mg group, that would have been statistically significant since a probability of .05 is the standard. A .05 probability means that there is only a one in twenty likelihood that the difference is due to random chance rather than a treatment effect. However, since there were two groups, probability needed to be .025 or a one in forty chance.

The general practice is to include dropouts in the final analysis; their last scores are included as results. If the per protocol group alone was considered (those who continued to the end of the trial and complied with the requirements), statistical significance was met for the 90 mg dosage group.

Statistical significance was achieved on the TMS. This was because of good results with eye movements and dystonia. There were no improvements in chorea. In addition, there were no statistically significant differences in cognition, behavior, or global assessments.

When all of the results are considered, the study was promising but it did not meet the standard for success which is statistical significance on the primary endpoint with inclusion of everyone who started the study.

Dr. Tedroff discussed the possibility that Huntexil, which is being tested for its potential to improve symptoms, might also slow disease progression. The effect is stronger in patients with higher CAG repeats, those who might be expected to progress faster. The effects seem to increase over time.

More data will be coming. There will be data from a six months open label extension of the Mermaid trial. The results of the North American HART trial will be available in October of this year. Basic research into the mechanisms of the drug will also continue.

The next two speakers were Dr. **Sarah Noonberg** from Medivation and Dr. **Francis Walker** from the Huntington Study Group. **Dimebon** was used as an antihistamine in Russia for many years but it also has some other potent pharmacological properties. Its precise mechanism of action is unknown but it enhances mitochondrial function and promotes neurite outgrowth.

In a study using primary rat cortical neurons, Dimebon improved neurite outgrowth in a dose dependent way and with results comparable to Brain Derived Neurotropic Factor (BDNF). In an HD drosophila model, Dimebon rescued photoreceptors from neurodegeneration in a dose dependent manner. Dimebon is being studied for improvement of symptoms but it is possible that it may improve disease progression.

Dr. Walker reported on the results of the Phase II trial. Dimebon was safe and well tolerated. There was an interesting indication of efficacy. The Dimebon group improved their scores on the Mini Mental States Exam (MMSE), not just compared to the placebo group but compared to their own baselines. These results were statistically significant, p = .008. This was remarkable given that all of the study participants had fairly high MMSE scores to begin with. However, there was no change in cognition as measured by the UHDRS or the AD cognitive test.

There was a trend in which behavior improved for the Dimebon group and worsened for the placebo group. However, this trend did not reach statistical significance.

The Phase III Dimebon trial, called Horizon, is now recruiting. This is a six months trial with centers in the U.S., Europe, and Australia. The primary endpoints are cognition and overall functioning. Secondary endpoints are behavior, motor symptoms, and independence in activities of daily living.

Information about the trial, the entry requirements and locations can be found here: http://www.horizontrial.com.

Dr. **Steven Hersch** spoke about the Phase III **creatine** trial, called **CREST-E**. This is a Phase III double blinded placebo controlled trial of high dose creatine in early Huntington's Disease. 650 participants will be enrolled at sixty Huntington Study Group sites and be followed for three years. So far 100 people have enrolled.

The study will answer three questions:

1. Is high dose creatine safe and well-tolerated for HD patients?
2. Can creatine slow down the progression of early HD by a minimum of 3 months per year?
3. Are there biomarkers that could make future clinical trials more efficient and successful?

Participants must:

- be 18 years old
- be capable of giving informed consent
- be in the early stages of HD
- have a diagnosis with a CAG test or be willing to take one
- agree to comply with study procedures
- not be pregnant, lactating, or planning a pregnancy

Participants may continue to take approved drugs during the trial.

Creatine targets energy. Levels of ATP are way down in mouse models of the disease and in human patients. ATP is a nucleotide that transports chemical energy within cells for metabolism. Creatine is converted to phosphocreatine which donates a phosphate group to ADP to produce ATP so creatine supplementation should produce more ATP.

Why is the dose so high? Athletes usually take between 3 and 5 grams but 20 to 40 grams is probably optimal for HD patients. Higher blood levels are needed to normalize levels of serum 8-hydroxy-2'-deoxyguanosine (8OH2'dG), a marker for oxidative damage to DNA.

Creatine was shown to slow brain atrophy in the Phase II trial.

The known side effects for creatine are GI upsets, nausea, diarrhea, edema, and weight gain. There is no known organ toxicity. Since we do not have experience with high doses, participants are being carefully monitored.

Since creatine is promising and is available over the counter, why shouldn't people with HD just go ahead and take it on their own instead of participating in the trial? First, creatine is regulated as a food rather than as a drug. That means that impurities are likely. Trial participants are receiving medicinal grade, FDA approved creatine. Second, patients should be medically monitored. Third, joining the trial will benefit the whole community.

If creatine is successful, it will be the first validation of a drug development paradigm based on efficacy in mouse models. It will also be the first compound for HD in which biomarker data (8OH2'dG) has established the optimal dose and shortened development. It is also set up to validate biomarkers for HD.

The study was funded primarily by the National Center for Complementary and Alternative Medicine. A smaller amount of funding was provided by the FDA's Office of Orphan Products Development. The biomarker part of the study is being funded by the FDA.

More information about the trial can be found here:
http://www.huntington-study-group.org/ClinicalResearch/ClinicalTrialsObservationalStudiesinProgress/CRESTE/tabid/105/Default.aspx
Participating sites are listed here:
http://www.huntington-study-group.org/Portals/0/CRESTESiteList.pdf

Dr. **Michael Liu** spoke about **Vertex's Huntington's Disease** drug development program. Vertex was founded in 1989. It has 1300 employees and five research and development sites. The San Diego site is working on pain, cystic fibrosis, and HD. They have drugs in Phase II and III trials for cystic fibrosis and hope to do the same for HD.

There are taking two approaches. One is direct targeting of the core defect, the HD protein. The other is neurorepair. He hopes to present at the next HDSA convention with news about potential treatments in the pipeline.

_____

Summary by Marsha L. Miller, Ph.D.
Photographs for this and the Research Forum update by Steven M. Ireland
July 6, 2010