Global Outcomes Data and Possible New Therapies in the Huntington's Pipeline

Researchers are focused on patient outcomes on a global scale and join clinicians in the vigil for new drug approvals.

A Q&A WITH GEORGE YOHRLING, PhD AND ED WILD, PhD

What were the biggest stories in Huntington's care this year?

Dr. Yohrling: Enroll-HD is the big story in terms of HD care. One of the major goals of this project is to acquire outcomes data on patients around the globe. These outcomes could help inform physicians about the best standard care practices that should be taken when caring for an HD patient.

While we wait for the next drug to be approved for HD, the biggest research story in my mind is the emergence of the global research platform/observational trial called Enroll-HD. My organization sees this as so crucial that, for the first time ever, Huntington's Disease Society of America formally endorsed this study and is urging the entire HD community to take part.

Development of an assay to detect fM levels of huntingtin protein in the CSF of HD patients is emerging from IRBM/Promidis. This is essential for huntingtin lowering trials to begin.

Another big story was the termination of the 2CARE clinical study for futility. The 2CARE (sponsored by Massachusetts General Hospital) study was evaluating the potential efficacy of CoEnzyme Q10 in HD. While disappointing for some, this is progress as it frees up over 600 patients for additional studies that have just begun.

Several new HD clinical trials from large pharmaceuticals are now underway, Including PDE10a inhibitors being tested by Pfizer and Omeros. Teva has also launched two trials in HD (pridopidine and laquinimod).

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Dr. Wild: In September the international GeM Consortium announced the preliminary findings of the largest ever genome-wide association study looking for genetic modifiers of age-at-onset in Huntington's disease. Any gene whose natural polymorphisms alter the course of HD can unmask new therapeutic targets that nature has already tested and proven to work in patients. GeM has analysed over 8,000 DNA samples from Europe and North America. Led by Prof. Leslie Jones of Cardiff University and Prof. Jim Gusella of Massachusetts General Hospital, GeM has the statistical power to surmount the shortcomings of previous genetic modifier work. Three chromosomal regions of interest, and their associated pathways, are now being closely studied.

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In clinical trial news, 2014 saw the announcement of no fewer than five new trials testing symptomatic and disease-modifying therapies, with the involvement of big names like Teva and Pfizer—a sign that the global HD community's intensive efforts are finally heralding a new era of therapies designed with HD in mind. Meanwhile interim 'futility' analyses of the huge 2CARE and CREST-E studies concluded that neither coenzyme Q10 nor creatine can delay progression in HD—disappointments for sure, but ones that allow informed decision-making for HD-affected people and their clinicians.

What were some of the important overlooked stories of 2014?

Dr. Yohrling: The Cicchetti et al. paper from May 2014 in *Annals of Neurology*[1] was pretty important in my mind but did not get a lot of discussion within community. They found that huntingtin aggregates were found in the unaffected transplanted fetal grafts that were placed into HD patients. This raises serious concerns about the potential spread of the bad protein in future stem cell transplantation studies.

Dr. Wild: There's a persistent view that Huntington's is a disease of the striatum—specifically, of its medium spiny neurons. This is understandable, since they die early and disproportionately in the disease. But mutant huntingtin is expressed ubiquitously and some pathological features like huntingtin aggregates and reduced brain-derived neurotrophic factor (BDNF) production are more prominent in the cortex. A beautiful study by William Yang studied the effect of selectively silencing the mutant gene in striatum, cortex or both. Yang's team found that silencing in either region was beneficial, and the best rescue came from reducing huntingtin in both cortex and striatum. This is an important proof of concept to inform the development of drugs targeting huntingtin expression in particular brain regions, and underscores the idea that HD is a whole-brain disease.[2]

What do you think 2015 has in store for Huntington's care? Are there any studies you're looking forward to?

Dr. Yohrling: The community is excited about the announcement from Isis Pharmaceuticals that their ASO against huntingtin is actually going to get its chance in the clinic with a Phase I study during the first half of 2015. The potential ASOs have as a disease-modifying therapy for HD is huge and has the patient community very excited and full of hope.

I believe 2015 will see an additional FDA approval for the management of chorea associated with HD. Auspex's First-HD and ARC-HD will be complete soon and I am hopeful that SD-809 will prove efficacious.

In terms of patient management, I am confident new approaches to telemedicine (such as smart phones, Skype and app development) will be tested in HD population.

Dr. Wild: If all goes to plan, 2015 will see Isis Pharmaceuticals launch a small clinical trial to assess the safety and tolerability of increasing dose levels of a targeted 'huntingtin protein lowering' drug in early HD patients. Called ISIS HTT-Rx, the compound is an antisense oligonucleotide—a single strand of chemically-modified DNA. Evidence to date from preclinical animal studies suggests that after intrathecal injection, ISIS HTT-Rx could achieve wide central nervous system distribution, bind very selectively to the mRNA transcribed from the HTT gene for translation into huntingtin protein, cause the degradation of this mRNA, and reduce production of the mutant huntingtin protein that is the known upstream cause of pathology in HD. The multinational trial's lead clinical investigator is Prof. Sarah Tabrizi at UCL Institute of Neurology. Targeted huntingtin lowering therapeutics are widely considered as one of the most promising therapeutic options, and this first-in-human safety trial represents a crucial first step on a much-anticipated journey. ■

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2. Wang N, Gray M, Lu X-H, et al. Neuronal targets for reducing mutant huntingtin expression to ameliorate disease in a mouse model of Huntington's disease. Nat Med 2014;20, 536–541