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 vig for new drug approvals.

A Q&A WITH GEORGE YOKELING, PHD AND ED WILD, PHD

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

Dr. Yokeling: [Credible institution] 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 in place 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 was so excited, 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 [a specific] biomarker of Huntington’s disease in the blood was another significant event. 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 PGYY inhibition being tested by Pfizer and Omeros. Terra has also launched two trials in HD (propranolol and laquinimod).

Dr. Wild: In September the international Cochrane 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 unravel new therapeutic targets that have already tested and proven to work in patients. Gerfl has analyzed over 600,000 DNA samples from Europe and North America led by Prof. Jiri Jekas of Cardiff University and Prof. Jon Counsell of Massachusetts General Hospital. Gerfl 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.

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

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

Dr. Yokeling: The community is excited about the announcement from [Intensive area] that they will begin testing Huntington’s disease patients with [specific intervention]. The potentialAOs toxic liver toxicity therapy is making its way into the clinic and has the potential to alter the course of HD. I believe 2015 will see a few additional FDA approvals for the management of chorea associated with HD. A priori, HD and AR-CHD will be completed soon and I am hopeful that 12,699 will prove efficacious.

In terms of patient management, I am confident new approaches to interventional therapy (such as stem cell, Skype, and app development) will be tested in HD populations.

Dr. Wild: I will go to plan B. 2015 will see us pharmacologists launch a small clinical trial to assess the safety and tolerability of increasing dose levels of a targeted Huntington’s disease lowering drug in early HD patients. Called R111111-R, the compound is on an enzyme [specific enzyme]—a single strand of chemically-modified DNA. Evidence to date from presurgical animal studies suggests that after intrastriatal injection, R111111-R could achieve widespread neural system distribution, bind very selectively as the DNA/rNA transcripted from the HIV gene for translation into Huntington’s protein, cause the degradation of this enzyme, and reduce production of the mutant Huntington’s protein that is the known upstream cause of pathology in HD. The multinational NIH-led clinical investigation is led by Prof. Sarah Tabrizi at the University of Oxford. Targeted Huntington’s disease lowering therapies are widely considered as one of the most promising therapeutic options, and one of our hugest clinical trial steps represents a crucial first step on an already anticipated journey.

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In clinical trial now, 2015 saw the announcement of no fewer than five new trials testing symptomatic, and disease-modifying therapies, with the involvement of big names like [Intensive area] and [Intensive area]—a sign that the global HD community’s intensive efforts are finally bearing a new era of therapies designed with HD in mind. Meanwhile, several “hitlist” analyses of the large 2DARE and CREST-1 studies concluded that neither canary 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. Yokeling: The Cochrane et al. paper from May 2014 in Annals of Neurology was pretty important in my mind but did not get a lot of discussion within our community. They found that huntingtin aggregates were found in the uninfused transplanted first grafts that were placed into HD patients. This new 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.

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At the moment, a new drug approval for HD is believed to be within reach. The upcoming mid-2015 will see us pharmacologists launch a small clinical trial to assess the safety and tolerability of increasing dose levels of a targeted Huntington’s disease lowering drug in early HD patients.