Early View

MOVING ALONG

International Parkinson and Movement Disorder Society

Moving Toward Target-Specific Therapies: What's New In Parkinson's Disease And Huntington's Disease

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While a cure is a pinnacle in therapeutics of neurodegenerative disorders, the field is not there yet. Disease-modifying therapeutics (DMTs) to slow disease progression and delay onset of advanced disease manifestations are urgently needed. Parkinson's disease (PD), the second most common neurodegenerative disorder with complex multifactorial pathophysiology of recognized heterogeneity, has a significant societal impact more than any other movement disorders. On the other hand, Huntington's disease is a rare neurodegenerative disorder associated with a fully penetrant autosomal dominant genetic mutation in the huntingtin (HTT) gene and provides a unique model for developing target-specific interventions.

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Fortunately, the pipeline is richer than ever in both PD and HD. A comprehensive review of PD experimental therapeutics (1) cited 145 active clinical trials including symptomatic and disease-modifying interventions and spanning Phase I (35%), Phase II (46%) and Phase III (19%) trials.

The current generation of DMTs in PD is much more grounded in disease biology, informed by recent discoveries in PD genetics and molecular biology and enhanced with an armamentarium of novel biomarkers (2). These attributes instill tremendous hope, though challenges remain. The two most active categories of development include alpha-synuclein and genetically targeted therapeutics. Multiple lines of data support the pivotal role of alpha-synuclein in PD pathogenesis, being the main constituent of Lewy bodies, the hallmark of PD pathology (3). The most advanced in clinical trial development are alpha-synuclein monoclonal antibodies targeting the extracellular protein. Results of the first two Phase II studies, PASADENA (NCT03100149) and SPARK (NCT03318523) were recently announced. Both studies did not meet the respective primary outcome(s). Contrary to SPARK trial, PASADENA 52 week results (4) document signals of efficacy in the secondary and exploratory digital outcomes.

Other efforts are ongoing in PD, including other monoclonal antibodies in earlier phases of development and targeting alpha-synuclein misfolding (UCB 0599, NCT04658186). Nilotinib postulated to increase alpha-synuclein clearance via stimulating autophagy, was evaluated in Phase 2 studies that did not confirm initial enthusiasm from a small open label study (5). Genetically-targeted therapeutics are very appealing as a DMT strategy, as it is applicable to PD subgroup sharing mutations in a causative or risk gene that are easily identified. Several GBA targeting therapeutics are in clinical development. MOVES-PD study testing the substrate-reducing drug venglustat (NCT02906020), is the most advanced trial and has not met primary or secondary outcomes. Other therapeutic approaches to rescue a dysfunctional GBA pathway are underway.

LRRK2-targeted therapeutics is perhaps of greatest impact in PD, as LRRK2-related PD is responsible for 3% of sporadic cases and up to 30% of familial cases in certain ethnic groups(6). There are two LRRK2 targeting therapeutic programs currently in clinical development. Small molecules LRRK2 inhibitors (DNL151 and DNL201) have completed Phase Ib studies (NCT04056689 and NCT03710707) and have advanced to a phase II/III study (7). An alternative approach is the use of antisense oligonucleotide (ASO) designed to bind to LRRK2 mRNA and thus reduce LRRK2 protein levels (NCT03976349).

HD has experienced a dramatic advance in the therapeutic development of DMTs in the last 5 years, mostly driven by genetically validated targets of the HTT gene (HTT-lowering therapies). More recently, somatic instability of HTT CAG repeat at an individual level started to be evaluated as a therapeutic target (SHIELD-HD, NCT04406636). HTT-lowering therapies represent a wide array of therapeutic strategies that target the biosynthesis of the mutated HTT protein at its different stages including transcription

repression, splicing modification, pre-mRNA clearance or translation inhibition. The two most advanced clinical programs include ASOs targeting the nuclear pre-mRNA of both mutated (mHTT) and wild-type HTT (GENERATION HD1; NCT03761849) or specifically the mHTT (PRECISION-HD1; NCT03225833 and PRECISION-HD2; NCT03225846). Both programs have recently reported negative results. The PRECISION-HD1/HD2 programs failed to report a robust target engagement with marginal reductions of CSF mHTT protein. The phase III trial GENERATION HD1 followed a positive IONIS-HTTRx first-in-human trial(8), and dosing has been terminated prematurely due to a worse progression in the group more frequently administered the active treatment(9). Further insights into these negative results are eagerly awaited to better understand its meaning and scope.

We have entered a new phase of DMT development, grounded in target-specific strategies. While recent results are disappointing, the field is poised to succeed. The road is challenging but better understanding of the disease biology will pave the way to success.

In the interim, clinicians may question whether we should focus on symptomatic therapies or DMT. To a large extent the dividing line is artificial. Until the time we develop DMT, any intervention that improves quality of life and/or reduces disability will have a meaningful impact on people living with these devastating diseases. The field is making progress, but the challenges remain.

References

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