Huntington’s Disease Drug Development

Subjects: Neurosciences

Contributor: Hannah J. Van de Roovaart , Nguyen Nguyen , Timothy D. Veenstra

Huntington’s Disease (HD) is a severely debilitating neurodegenerative disorder in which sufferers exhibit different combinations of movement disorders, dementia, and behavioral or psychiatric abnormalities. The disorder is a result of a trinucleotide repeat expansion mutation that is inherited in an autosomal dominant manner. While there is still no treatment to alter the course of HD, there are medications that lessen abnormal movement and psychiatric symptoms.

Huntington’s disease treatment clinical trial

1. Introduction

Huntington’s Disease (HD) is a rare autosomal dominant neurodegenerative genetic disorder that has an average onset between 30 and 50 years of age [1]. The worldwide prevalence of HD is approximately 7 in 100,000 persons, with further evidence suggesting the worldwide prevalence may be increasing [2][3][4][5][6]. The regions of highest prevalence are North America and the United Kingdom, with Asia having the lowest [4]. This disease places a heavy cost burden on patients, caregivers, and the health system. A recent Huntington’s Disease Burden of Illness study comprising patients from five European countries and the United States estimated the annual direct medical, nonmedical, and indirect costs associated with HD at just over EUR 63,000 (i.e., about USD 68,000) per patient per annum [5]. Predictably, these costs escalate as patients progress from early- to late-stage HD. Hospital visits and long-term care account for the largest proportion of these expenses.

Caused by a mutation in the Huntington gene (*HTT*), HD patients have what is known as a “CAG repeat expansion,”. While most healthy people have between 10 and 30 repeats, individuals with HD have 40+ CAG repeats [7]. This trinucleotide repeat inserts additional glutamine residues (referred to as a polyQ domain) within the translated huntingtin protein (HTT). The average age of onset is between 30 and 50 years of age, with individuals possessing longer trinucleotide repeats generally exhibiting symptoms of HD at earlier ages [8]. In predictive models, the length of the trinucleotide repeats accounts for about 70% of the interpatient variability in the age of onset [9]. The highest concentrations of HTT are located within the brain and testes [10]. The main functions of HTT involve chemical signaling, cellular dynamics (i.e., the cytoskeleton, endocytosis, trafficking, and adhesion), metabolism, protein turnover, gene expression (transcription and RNA processing), and protection [11][12]. The aggregation of mutant HTT (mHTT) is the main pathophysiological signature of patients with HD [13]. These aggregates form inclusion bodies inside cells that lead to cell quiescence and neuronal degeneration [14][15]. The clinical manifestations of HD include chorea, dementia, and psychiatric symptoms that eventually lead to death between 15 and 20 years after symptoms are first detected [16][17].

While HD affects the entire brain, there is evidence of enhanced vulnerability within the striatum, which is part of the basal ganglia [18]. This brain region is involved in motor control, emotion, habit formation, and reward [19]. Neuronal degeneration within the basal ganglia is consistent with the symptoms observed in HD patients that include memory impairment, slurred speech, chorea, weight loss, and personality changes [20][21][22].

2. Huntington's Disease Drug Development

ClinicalTrials.gov was used to identify drugs that are currently in or have recently completed a phase III trial for an indication within HD. Only interventional phase 3 trials that were recruiting patients, were active but not recruiting patients, or had been completed were included. All the studies must have had an update posted within the past year.

Nine clinical trials were identified in accordance with the aforementioned criteria. There are eight different drug interventions included in the nine clinical trials. Four of these medications (dextromethorphan/quinidine, valbenazine, deutetrabenazine, and metformin) are FDA approved for alternative indications while four others (Cellavita HD, pridopidine, tominersen, and SAGE-718) have not yet been marketed and are seeking their first FDA approval.

The nine drugs described herein, along with some brief clinical trial information, are listed in **Table 1**.

Table 1. List of phase III clinical trials testing the effects of various drugs in the treatment of Huntington's Disease.

Drug	Clinical Trial Name	Identifier	Primary Outcome
Metformin	Testing METformin against cognitive decline in HD	NCT04826692	Evaluate drug's effect on scores obtained in different cognitive subtests that make up the Unified Huntington's Disease Rating Scale (UHDRS)
Dextromethorphan/ quinidine	Evaluating the Efficacy of Dextromethorphan/Quinidine in Treating Irritability in HD	NCT03854019	Measure patient's irritability using The Irritability Scale
Deutetrabenazine	Impact of Deutetrabenazine on Functional Speech and Gait Dynamics in Huntington Disease	NCT04713982	Improvement on Sentence Intelligibility Test and Motor Speech Evaluation
Valbenazine	Efficacy, Safety, and Tolerability of Valbenazine for the Treatment of Chorea Associated with Huntington Disease (KINECT-HD)	NCT04102579	Improvement in chorea symptoms and evaluation of treatment-emergent adverse events
	An Open-Label Rollover Study for Continuing Valbenazine Administration	NCT04400331	Evaluation of treatment-emergent adverse events

Drug	Clinical Trial Name	Identifier	Primary Outcome
	for the Treatment of Chorea Associated With Huntington Disease		(TEAEs)
Cellavita HD	Clinical Extension Study for Safety and Efficacy Evaluation of the Cellavita HD Product in Huntington's Patients (ADORE-EXT)	NCT04219241	Evaluate treatment's effectiveness as verified by comparing the total UHDRS
Pridopidine	Pridopidine's Outcome on Function in Huntington Disease, PROOF-HD	NCT04556656	Measure change from baseline in UHDRS-Total Functional Capacity score
SAGE-718	A Study to Evaluate the Safety and Tolerability of SAGE-718 in Participants With Huntington's Disease	NCT05655520	Measure number and severity of TEAEs Measure number of participants that withdraw due to adverse events Measure change from baseline in clinical laboratory and electrocardiogram parameters Measure change in baseline in C-SSRS responses
RO7234292 (RG6042)	An Open-Label Extension Study to Evaluate Long-Term Safety and Tolerability of RO7234292 (RG6042) in Huntington's Disease	NCT03842969	Measure number and severity of TEAEs Measure number of participants with suicidal ideation/behavior and self-injurious behavior without suicidal intent based on C-SSRS scale Measure change from baseline in MoCA

Metformin is one of the oldest and most studied diabetic medications [23][24]. Besides type 2 diabetes (DM2), metformin may also offer cardiovascular protection and beneficial effects on obesity, musculoskeletal and reproductive diseases, cancer, and aging [25]. Not only is metformin able to penetrate nearly every bodily organ, it is also a well-known pleiotropic agent that modulates a plethora of metabolic pathways, extending its possible use beyond already FDA-approved indications [26]. The major molecular targets of metformin include complex I of the mitochondrial electron transport chain, the mechanistic target of rapamycin complex 1 (mTORC1), and adenosine monophosphate-activated protein kinase (AMPK) [27]. The interest in metformin as an HD treatment is in its ability to activate AMPK. Located throughout the body, this enzyme induces improved neuronal survival by inhibiting inflammation and promoting cell renewal processes [28]. Metformin has also been shown to induce autophagy, inhibit mHTT aggregation, and reduce the accumulation of this mutant protein within an HD mouse model [29]. While metformin activation of AMPK may offer some benefits, the optimal timing of AMPK activation appears to be an important variable in its effectiveness as an HD therapeutic. Data from in vivo/in vitro models and analyses of brain tissue have demonstrated that AMPK activation during late stages of HD could have negative effects [30]. Thus, AMPK may be an efficacious target in early-stage HD but may have contrasting effects during late-stage HD.

2.2. Dextromethorphan/Quinidine

Dextromethorphan/quinidine (DM/Q) is a fixed-dose combination therapy that was approved by the FDA in 2010 [31]. It is marketed by Avanir Pharmaceuticals under the brand name Nuedexta. Dextromethorphan is a noncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist and a sigma-1-receptor (S1R) agonist [32]. Quinidine prolongs the plasma levels of dextromethorphan by inhibiting the CYP2D6 enzyme. There is evidence that NMDA receptor excitotoxicity is implicated in the pathogenesis of HD. Enhanced NMDA receptor signaling is detected at ages prior to motor dysfunction and neuronal loss. Specifically, agents such as quinolinic acid (a selective NMDA receptor agonist) can produce striatal degeneration. There are studies in HD mice treated with NMDA receptor antagonists that showed the reversal of nuclear signaling and motor learning deficits. Pridopidine, an S1R agonist, has previously been shown to have neuroprotective effects in cellular and animal models of HD (as well as Alzheimer's Disease) presumably by increasing mitochondrial activity. This increased activity led to improvements in motor coordination and a delay in symptom onset in mouse HD models.

2.3. Deutetrabenazine

As a reversible inhibitor of vesicular monoamine transporter 2 (VMAT2), deutetrabenazine decreases the reuptake and stores monoamines (i.e., dopamine, serotonin, histamine, and norepinephrine) within presynaptic vesicles [33]. VMAT2 is located on the synaptic vesicles of presynaptic neurons [34]. Responsible for the packaging and release of monoamines into the synapse, drugs targeting this transporter have shown efficacy in treating symptoms that manifest from the imbalance of monoamines [35].

Deutetrabenazine is a deuterated form of tetrabenazine, meaning that there is a substitution with deuterium for hydrogen throughout the molecule, giving it a plasma half-life (t½) almost two-fold greater than tetrabenazine [36]. This longer t½ decreases plasma fluctuations, resulting in fewer adverse effects such as somnolence, insomnia, depression, and Parkinsonism, which are associated with peak drug concentration.

2.4. Valbenazine

Hyperkinetic movements including those representative of chorea have been associated with high dopamine states. Thus, the current standard of care aims to decrease dopamine activity through the off-label use of antipsychotics that antagonize postsynaptic receptors or the on-label use of the existing FDA-approved VMAT2 inhibitors deutetrabenazine and tetrabenazine [37]. As a VMAT2 inhibitor, valbenazine works similarly to deutetrabenazine and tetrabenazine to treat chorea associated with HD. Valbenazine differs from deutetrabenazine and tetrabenazine in its affinity for VMAT2. Deutetrabenazine and tetrabenazine are broken down into four different stereoisomers, all of which have shown varying affinity for VMAT2. Valbenazine is broken down into only one stereoisomer, [+]-α-dihydrotetrabenazine, which has the strongest affinity for VMAT2 of all the stereoisomers [37]. In addition to the affinity observed with respect to VMAT2 receptors, valbenazine's formulation allows for easier titration and daily dosing. Deutetrabenazine and tetrabenazine require multiple episodes of daily dosing, with tetrabenazine specifically requiring a slower, more complicated uptitration schedule.

2.5. Cellavita HD

Cellavita HD represents a novel therapy within the treatment landscape for HD. Cellavita HD is a stem cell therapy that may help restore lost brain cells [38]. Cellavita HD involves dental-pulp-derived mesenchymal stem cells that have been associated with both multifaceted differential effects as well as immunomodulatory functions [39]. Capable of crossing the blood–brain barrier, Cellavita HD promotes the proliferation of neuronal stem cells. Available evidence supporting the use of dental pulp stem cells in neurodegenerative disorders comes from their ability to regulate different molecular mediators including those within the anti-inflammatory, neurogenic, antiapoptotic, angiogenic, and osteogenic classes [40].

2.6. Pridopidine

In HD, there is progressive neuronal loss in the striatum. This process includes the dysregulation of endoplasmic reticulum (ER) calcium, altered mitochondrial function, reduced autophagy, increased ER stress, and reduced brain-derived neurotrophic factor, all ultimately leading to neuronal death [41]. Pridopidine was originally identified as a low-affinity dopamine D2 receptor ligand that modulated dopamine-dependent behaviors [42]. In the R6/2 mouse model of HD, pridopidine had been shown to improve motor performance and offer neuroprotective effects [43]. Recent evidence, however, has shown that pridopidine's affinity for S1R is ~100- and ~30-fold higher than that for the D2 and D3 receptors, respectively [42]. These results suggest that the positive effects of pridopidine are modulated through its interaction with S1R. Studies have shown that pridopidine activation of S1R reduces cell stress and inflammation, while increasing cellular energy production and the clearance of toxic proteins. Since S1R is also involved in synapse plasticity, pridopidine can enhance neuronal connectivity. Prilenia Pharma currently holds orphan drug designation for the treatment of HD in both the US and EU using pridopidine, while simultaneously receiving fast-track designation from the FDA [44].

2.7. SAGE-718

After receiving orphan drug status and fast-track designation for the treatment of HD by the European Medicine Agency, SAGE-718 has gained traction in both its clinical development and regulatory review process. As a first-in-class NMDA receptor modulator, SAGE-718 was designed to improve cognitive function in disorders associated with NMDA dysfunction such as AD and HD [45]. Modulation of the NMDA receptor enhances long-term effects at neuronal synapses, which is an essential process in learning and memory.

2.8. Tominersen (RO7234292 or RG6042)

Tominersen is also known as RO7234292 or RG6042. Ionis Pharmaceuticals designed tominersen and licensed the treatment to Roche, who is currently developing and marketing it as a potential HD treatment. Tominersen is an antisense RNA that binds to mRNA transcribed from the mutant *HTT* gene found in HD patients. This interaction creates an *HTT* mRNA/tominersen hybrid, which is degraded by the cell and is therefore not translated into the mHTT protein (**Figure 1**). The net result is a reduced production of mHTT.

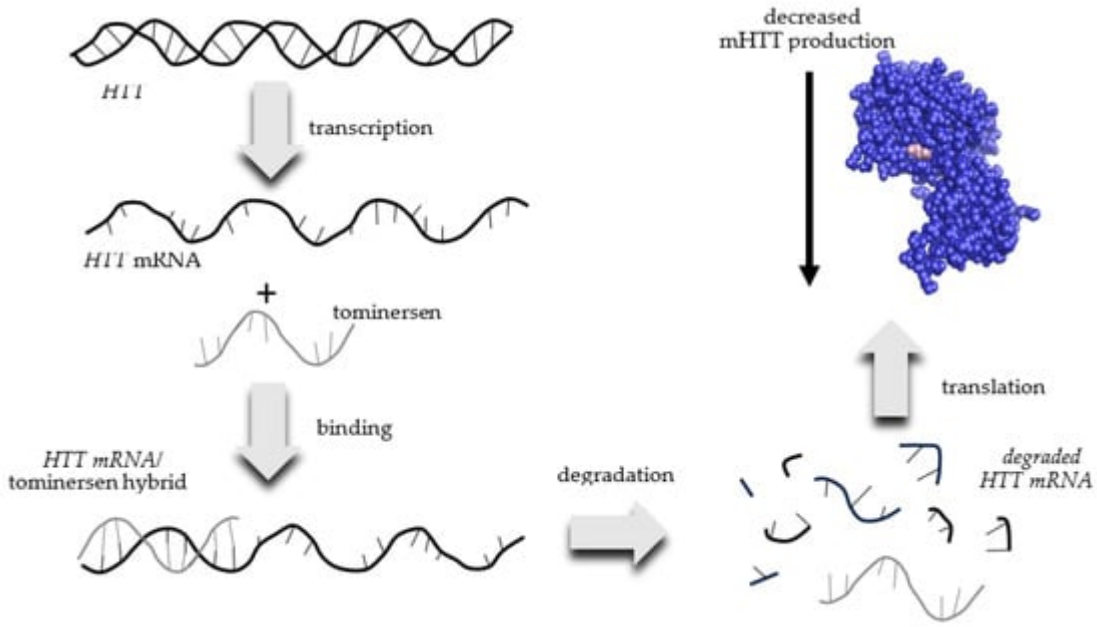

Figure 1. Mechanism of action of tominersen for the decreased production of mutant huntingtin (mHTT) protein in patients with Huntington’s Disease.

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