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REVIEW

Therapeutic Update on Huntington's Disease: Symptomatic Treatments and Emerging Disease-Modifying Therapies

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Abstract

Huntington's disease (HD) is a monogenic neurodegenerative disorder that presents with progressive motor, behavior, and cognitive symptoms leading to early disability and mortality. HD is caused by an expanded CAG repeats in exon 1 of the huntingtin (HTT) gene. The corresponding genetic test allows a clinical, definite diagnosis in life and the identification of a fully penetrant mutation carrier in a premanifest stage. In addition to the development of symptomatic treatments that attempt to address unmet care needs such as apathy, irritability, and cognition, novel therapies that target pathways specific to HD biology are being developed with the intent of slowing disease progression. Among these approaches, HTT protein lowering therapies hold great promise. There are currently active programs using antisense oligonucleotides (ASOs), RNA interference, small-molecule splicing modulators, and zinc-finger protein transcription factor. Except for ASOs and RNA interference approaches, the remaining therapeutic strategies are at a preclinical stage of development. While the current therapeutic landscape in HD may bring an unparalleled change in the lives of people with HD and their families with the first-ever disease-modifying therapy, the evaluation of these therapies requires novel tools that enable a more efficient and expedited discovery and evaluative process. Examples are biomarkers targeting the HTT protein to measure target engagement or disease progression and rating scales more sensitive to the earliest clinical changes. These tools will be instrumental in the next phase of disease-modifying clinical trials in HD likely to target the phenoconversion period of the disease, including the prodromal HD stage.

Key Words Huntington's disease · chorea · disease modification · therapies

Introduction

Huntington's disease (HD) is an autosomal-dominant neurodegenerative disorder with an estimated worldwide prevalence of 2.7 per 100,000 [1], with a lower prevalence in Asia [1], and prevalence as high as 12.3 to 13.7 per 100,000 in countries like Canada and the UK [2, 3]. HD is caused by an expanded CAG repeats in exon 1 of the huntingtin (*HTT*) gene, which leads to the synthesis of a mutant form of the huntingtin protein (mHTT) [4]. The availability of a clinical test to identify the gene mutation allows to confirm a clinical diagnosis of HD in life (CAG $n \geq 36$) and to identify those individuals that carry the mutation and will develop the disease (CAG $n \geq 40$). A longer CAG repeat length is associated with an earlier onset and faster clinical progression [5].

The clinical hallmark of the disease is the presence of chorea, together with the nonmotor features of cognitive decline and behavioral changes such as apathy, depression, irritability, anxiety, obsessive/compulsive behaviors and, more rarely, psychosis [6]. Parkinsonism is a later feature in adult-onset HD and a presenting feature in the juvenile form of HD [4]. Symptoms progress relentlessly over time and leads to death in 10–15 years from clinical onset [7]. In the last couple of decades, observational studies highlighted the presence of subtle cognitive and behavioral changes together with structural brain abnormalities many years before the appearance of classic motor features that more commonly allow clinical

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diagnosis [8, 9]. These findings led to the definition of discrete periods in the natural history of HD in relation to symptom onset. The recent classification proposed by the HD Task Force of the International Parkinson's Disease and Movement Disorder Society established three diagnostic categories (presymptomatic HD, prodromal HD, and manifest HD) according to the presence and severity of motor and cognitive changes [10]. Importantly, each diagnostic category was associated with the potential for the development of novel symptomatic and/or disease-modifying therapies [10].

The drug development approach for HD has undergone a remarkable evolution in recent years. Aside from efforts focused on symptomatic treatment, therapies that target specific aspects of HD biology are being developed and evaluated for the first time for a putative slowing of disease progression. In this review, we provide an update on the advances in the symptomatic treatment of HD and present the growing efforts in disease-modifying therapies, with a particular emphasis on interventions aimed at lowering the level of mHTT in the brain.

Symptomatic Treatment

The multifaceted clinical presentation of HD makes symptomatic management challenging, with the need for multiple treatments and the intervention of a multispecialty care team. The first systematic review on therapeutic interventions for HD concluded that tetrabenazine (TBZ) is the only drug with evidence for the treatment in HD, specifically for chorea [19]. Consequently, the symptomatic treatment in HD continues to be mostly based on expert opinion, the extrapolation of the best evidence available for other conditions, and good clinical practice recommendations. In this section, we provide an update on the efforts to develop an evidence-based approach to symptom-based treatment in HD divided into its different symptom clusters. (Table 1).

Motor Symptoms Symptomatic therapeutic development has focused primarily on chorea and motor impairment using as outcome measures the Unified Huntington's Disease Rating Scale (UHDRS) total motor score or its chorea items. Chorea is the clinical feature in HD for which most of the therapeutic studies have been conducted [19] and remains the only HD symptom for which there is a formal therapeutic indication. There are no approved treatments for the other motor features.

TBZ is an inhibitor of the vesicular monoamine transporter 2 (VMAT2) and the first drug with an FDA-approved indication for HD. This indication was supported by a 12-week randomized controlled trial (RCT) TETRA-HD [20] that documented a clinically significant reduction of chorea with TBZ compared with placebo, with an adjusted decrease of 3.5 points in the UHDRS chorea subscore [20]. There was no benefit in terms of functional ability [20]. The most common dose-limiting side effects for TBZ were somnolence, insomnia, depressed mood, akathisia, and parkinsonism [20]. More recent studies have demonstrated the long-term efficacy and tolerability of TBZ in patients with HD [21].

Deutetrabenazine (deuTBZ), a deuterated version of TBZ, was recently approved by the FDA for the treatment of chorea in HD. The introduction of a deuterated form of hydrogen molecules in deuTBZ imparts a longer half-life, with less frequent daily dosing and potentially better tolerability than TBZ [22]. With this rationale, the RCT FIRST-HD demonstrated a 12-week efficacy with a 2.5-point reduction in the UHDRS chorea subscore compared with placebo and a similar rate of depression, anxiety, and akathisia in deuTBZ and placebo arms [23]. There is no head-to-head comparison study of TBZ and deuTBZ. A network meta-analyses of FIRST-HD and TETRA-HD studies concluded similar antichoreic effect and safety, except for less depression and somnolence with deuTBZ [24]. An indirect treatment comparison reported less neuropsychiatric side effects and risk of akathisia and parkinsonism with deuTBZ compared to TBZ [25].

The overnight switch from TBZ to deuTBZ was safe and well-tolerated in the ARC-HD open-label safety study [26]. The single daily dosing VMAT2 inhibitor valbenazine is under evaluation for the treatment of chorea (NCT04102579, KINECT-HD) [27].

Other interventions have been investigated for the treatment of chorea in HD. Neuroleptics and amantadine were evaluated in small RCTs [28], and the evidence is less robust. In an international survey, TBZ and dopamine-blocking agents were commonly used in clinical practice to treat chorea in HD [29]. There was no consensus regarding the use of amantadine for chorea. Benzodiazepines were found to be useful as an adjunctive therapy for chorea exacerbated by anxiety [30]. As a good clinical practice recommendation, the treatment of chorea should be considered to improve functional ability and not solely to reduce its severity. Because of the progressive nature of the illness, the dose and use of medications needs to be reassessed periodically [30].

Surgical interventions have been considered for severe refractory chorea. HD was at the forefront in human stereotactic neurosurgery, with the first pallidal neurosurgery being conducted in a patient with clinical HD for the relief of chorea [31]. With the advent of neuromodulation, pallidal deep brain stimulation (DBS) has been evaluated in small noncontrolled studies [32–38]. A double-blind, randomized crossover study of pallidal DBS demonstrated a significant improvement in chorea, quality of life, and functional scores at a 6-month follow-up, but not for dystonia [39]. Unfortunately, pallidal DBS can be associated with the worsening of parkinsonism and gait [39–41]. A larger sham-controlled, multicenter RCT (HD-DBS) is currently ongoing to assess the impact of pallidal DBS for chorea and other aspects of the HD motor phenotype (NCT02535884) [42].

Other movement disorders in HD remain orphan therapeutic indications in need of further trials. There is a dearth of

Table 1 Recent and ongoing studies for symptomatic treatment for various symptoms of Huntington's disease. (Only randomized controlled trials were included)

Indication	Compound	Mechanism of action	Name of the study	Registration ID (last date of update)	Results
Motor impairment	PF-02545920	Phosphodiesterase 10A inhibitor	Amaryllis	NCT02197130 (November 2017)	Completed Safe and well-tolerated [11]
	PF-02545920	Phosphodiesterase 10A inhibitor	APACHE	NCT01806896 (December 2017)	Completed Worsening of chorea [12]
	Pridopidine	Dopamine stabilizer Sigma 1 receptor agonist	PRIDE-HD	NCT02006472 (March 2019)	Completed Negative for efficacy [13]
	SOM3355	Vesicular monoamine transporter 2 inhibitor	–	NCT03575676 (September 2019)	Completed Results not in public domain
	Triheptanoin	Anaplerotic therapy	TRIHEP3	NCT02453061 (July 2019)	Ongoing Not recruiting
Chorea	Risperidone	Dopamine antagonist	–	NCT04201834 (April 2020)	Not yet recruiting
	Valbenazine	VMAT2 inhibitor	Kinect-HD	NCT04102579 (May 2020)	Ongoing Recruiting
	AFQ056	Metabotropic glutamate receptor 5 antagonist	–	NCT01019473 (September 2011)	Completed Safe and well-tolerated Negative for efficacy [14]
	Pallidal stimulation (DBS)	Neuromodulation	HD-DBS	NCT02535884 (August 2019)	Ongoing Recruiting
	Pallidal stimulation (DBS)	Neuromodulation	–	NCT04244513 (January 2020)	Not yet recruiting
	PINS Stimulator System	Neuromodulation	–	NCT02263430 (October 2016)	Recruitment status unknown
Irritability	SRX246	Vasopressin 1a receptor antagonist	STAIR	NCT02507284 (October 2019)	Completed No results in public domain
	Dextromethorphan/quinidine	Morphinan/class I antiarrhythmic agent	–	NCT03854019 (April 2019)	Ongoing Recruiting
Apathy	Bupropion	Norepinephrine/dopamine reuptake inhibitor	Action-HD	NCT01914965 (September 2014)	Completed Negative for efficacy [15]
Cognition	PBT2	Inhibition of metal-induced aggregation of mHTT	–	NCT01590888 (July 2016)	Completed Safe and well-tolerated [16]
	(2)-Epigallocatechin-3-gallate	Polyphenol	ETON	NCT01357681 (June 2015)	Completed No results in public domain
	Neflamapimod	p38α MAPK inhibitor	–	NCT03980938 (July 2019)	Ongoing Recruiting
	SAGE-718	NMDA receptor modulator		NCT03787758 (November 2019)	Completed Safe and well-tolerated (n = 10 HD patients) Phase II study announced [17]
Functional ability	Varenicline	Nicotinic agonist	VCAS-HD	ACTRN12616001611415 (November 2016)	Ongoing
	Cannabinoid mixture	Reduce inflammation and oxidative stress	–	NCT01502046 (February 2013)	Completed Safe and well-tolerated Negative for efficacy [18]

literature to inform evidence-based treatment for parkinsonism or dystonia in HD. For example, dopaminergic agents have been considered for parkinsonism in the juvenile form of HD, but the evidence is based mostly on case reports [43, 44]. More recently, a case series evaluated the use of cannabinoids for the treatment of dystonia in HD with a reported improvement in the UHDRS dystonia items, using a prepost design without a comparator group [45].

Behavioral Symptoms Behavioral changes are a core feature of HD associated with poor quality of life in patients and a source of stress for relatives and caregivers alongside cognitive impairment [46]. There is very little data from clinical trials to guide the management of behavioral symptoms in HD. In the recent past, buspirone was evaluated in an RCT for the treatment of apathy with negative results [15]. Currently, dextromethorphan/quinidine and SRX46, a vasopressin 1A receptor antagonist, are being evaluated for irritability (Table 1).

Without contributory evidence from RCTs, guidelines for the treatment of behavioral symptoms in HD are based on expert consensus [47–49]. In depression, psychotherapy and cognitive behavioral therapy could have a role in early milder forms. Serotonin reuptake inhibitors (SSRIs) and serotonin–norepinephrine reuptake inhibitors are the first-line pharmacological options for both depression and anxiety. Although SSRIs can have a role for irritability, the use of sedative antidepressants, neuroleptics, or mood stabilizers is considered in more severe cases. Apathy remains a difficult symptom to treat in HD. A trial of an antidepressant is reasonable, particularly when depression coexists [47].

Cognitive Symptoms The evidence for the treatment of cognitive symptoms is minimal and derives from small RCTs. A Cochrane review of acetylcholinesterase inhibitors for HD included data from two RCTs in a total of 48 HD subjects. It concluded that the efficacy of cholinesterase inhibitors for cognitive dysfunction is unclear [50]. A couple of RCTs are ongoing with the compounds neflamapimod (MAPK inhibition) and SAGE-718 (NMDA receptor modulation). (Table 1).

Emerging Therapies for Disease Modification in HD

In the past decades, there have been various efforts to identify disease-modifying therapies in HD. Overall, these compounds targeted multiple downstream cellular processes and molecular targets, including oxidative stress, transcriptional dysregulation, mitochondrial dysfunction, and excitotoxicity [51]. Unfortunately, these clinical trials did not result in a disease-modifying therapy for HD [51].

The field of HD therapeutics lives through promising times as novel interventions targeting proximal pathways in the HD cell pathogenesis, such as the synthesis of mHTT and its intracellular trafficking, are evaluated for a disease-modifying effect. The ability to inhibit the synthesis of mHTT is perhaps the therapeutic strategy with the highest potential for disease modification. Various mHTT-lowering approaches are at a preclinical phase, and a few clinical trials have already started in some programs (Table 2). In the following section, we provide an updated description of various therapeutic development programs aiming at identifying a disease-modifying treatment in HD, with a particular focus on approaches targeting the HTT pathway.

HTT-Targeted Approaches

The CAG repeat expansion in the HTT gene found in HD leads to the transcription of a pathologically long pre-mRNA and the synthesis of an abnormal and unstable mHTT protein [60]. Although the precise role of mHTT in the pathophysiology of HD is not entirely clear, the overall effect of mHTT is associated with a toxic gain -of-function in various biological functions such as transcription, intracellular signalling, intracellular transport, mitochondrial function, synaptic dysfunction, and even immunity [4]. Different species of mHTT can contribute to its toxic effect from the full-length protein to fragments at N-terminal end, exon 1, expansion proteins from a repeat-associated non-ATG translation mechanism [61]. The relative importance of the different mHTT species may determine the success of HTT-targeted strategies.

Since the seminal paper of Yamamoto et al. demonstrated that mHTT suppression in HD mouse models could reverse neuropathological and the motor phenotype [62], various therapeutic strategies have been designed to target the HTT pathway to eliminate or, at least, lower the levels of mHTT in the brain. These strategies target the HTT cell lifecycle at the level of the DNA, RNA, or the protein itself. DNA-based strategies include removing the mutated gene from the genome (clustered regularly interspaced short palindromic repeats (CRISPR)-Cas9 gene-editing system) or inhibiting its transcription. RNA-based approaches inhibit the transcription process and synthesis of mHTT, whereas protein-based strategies modulate the mHTT protein homeostasis.

RNA-Targeted Therapies

The process of HTT synthesis can be modulated by targeting pre-mRNA using antisense oligonucleotides (ASOs), interfering with the splicing process using small-molecule splicing modulators or inhibiting coupling of mRNA to the ribosome using RNA interference (RNAi) strategies. These approaches promote cleavage, enhanced degradation, or translational suppression of mHTT mRNA resulting in a reduction of mHTT protein that may slow disease progression in HD [61].

Table 2 Huntingtin-lowering programs targeting DNA and RNA

Compound	Stage of development (study ID)	Delivery	Advantages	Disadvantages	Clinical results
DNA-targeting approaches					
Zinc-finger transcription factor					
Takeda/Sangamo NOS [52]	Preclinical	Intracranial*	Single treatment can provide long-term effects Applicable to all HD mutation carriers May cover all pathogenic mechanisms	Invasive delivery Irreversible effect Restricted diffusion in the brain Immunogenicity of nonhost protein	n/a
Imperial College London [53, 54]	Preclinical	Intracranial*	Same as above Lesser immunogenic effect, with use of host species proteins	Invasive delivery Irreversible effect Restricted diffusion in the brain	n/a
CRISPR/Cas9					
Emory University [55]; University of Pennsylvania [56]; Harvard University [57]	Preclinical	Fibroblasts [55, 56] Intrathecal [57]	Highly specific and targeted May cover all pathogenic mechanisms	Irreversible effect Ethical concerns Invasive delivery Immunogenicity of bacterial proteins Effect on germline	n/a
RNA-targeting approaches					
Antisense oligonucleotide					
RG6042/tominersen	Phase Ia/2 (NCT02519036)	Intrathecal	Applicable to all HD mutation carriers	Unknown risks of wild-type HTT Repeated lumbar punctures	First-in-human study Safe and well-tolerated [58]
RG6042/tominersen	Phase III (NCT03761849)	As above	As above	As above	Ongoing Recruitment concluded
WVE-120101; WVE-120102	Phase Ib/2a (NCT03225833; NCT03225846)	Intrathecal	Target mutant allele	Applicable to a group of HD mutation carriers (SNP-specific) Repeated lumbar punctures	Preliminary results: safe and mean reduction of 12.4% in CSF mHTT [59]
Biomarin NOS	Preclinical	Intrathecal	Target mutant allele with a single drug for all HD mutation carriers	Greater risking of off-target effects Repeated lumbar punctures	n/a
RNA interference					
AMT-130 (miRNA)	Phase I/II (NCT04120493)	Intracranial*	Nonselective miRNA Single treatment can provide long-term effects	Invasive delivery Irreversible effects Restricted diffusion in the brain Neutralizing antibodies	n/a
VY-HTT01 (miRNA)	Preclinical	Intracranial*	As above	As above	n/a
Spark NOS	Preclinical	Intracranial*	As above	As above	n/a
ALN-HTT (siRNA)	Preclinical	Implantable pump for intracranial infusion system	–	–	n/a

Table 2 (continued)

Compound	Stage of development (study ID)	Delivery	Advantages	Disadvantages	Clinical results
Small-molecule splicing modulators					
PTC-CHDI NOS	Preclinical	Oral	Ease of delivery Potentially reversible	Nonselective approach targeting total HTT Off-target effects	n/a
Skyhawk-Novartis NOS	Preclinical	Oral	–	–	n/a

NOS = not otherwise specified; n/a = not available

*Adeno-associated virus (AAV) as a vector

Antisense Oligonucleotides ASOs are synthetic single-stranded synthetic oligonucleotide analogues ranging from 16 to 22 nucleotides that hybridize with complementary RNA sequences and can prevent protein synthesis, alter transcript processing [63], or prevent the mRNA translation with an early degradation via ribonuclease H-mediated hydrolysis [64]. ASOs are classified into those targeting solely the mutated HTT mRNA (allele-specific) or those targeting wild-type and mutated HTT mRNA (nonallele-specific). ASOs have demonstrated reversal of the HD pathology and clinical phenotype in preclinical studies laying the basis of clinical trials for these approaches [65–67].

The first ASO to be tested in clinical studies was the nonallele-specific ASO RG6042, now known as tominersen. Leading up to first-in-human clinical trials, ASOs demonstrated a reduction of up to 80% of the mHTT mRNA expression and 60% of the mHTT protein with the rescue of the HD phenotype in various animal models [65–67]. The IONIS-HTTRx study was the first-in-human clinical trial and assessed safety, tolerability, pharmacokinetics, and pharmacodynamics of multiple ascending doses of tominersen up to 120 mg with four monthly intrathecal administration in a total of 46 subjects with early manifest HD [58]. The pharmacokinetics and pharmacodynamics were conducted on CSF and plasma samples. There was a dose-dependent mean reduction of about 40% in CSF mHTT concentration at the two highest doses of 90 to 120 mg of tominersen [58], which may correspond to a 55 to 85% reduction in cortical mHTT and a 20 to 50% reduction in caudate mHTT [68]. A persistent effect was established in the subsequent 2-month follow-up period. There were no significant safety concerns or dose-limiting toxicity. *Post hoc* analyses suggested a correlation between a reduction in CSF mHTT and improvement in a composite UHDRS score. However, these results should be interpreted with caution as the trial was not primarily designed to document a clinical benefit. A phase III multinational, multicenter trial enrolling more than 800 subjects in early manifest HD is currently ongoing to provide confirmatory efficacy data for tominersen as a disease-modifying therapy (GENERATION-HD1, NCT03761849) [69].

Allele-specific ASOs have also entered the clinical trial phase. Allele specificity is obtained by targeting individual single nucleotide polymorphisms (SNPs) found in the mutated HTT gene [70]. These SNPs are present in not all but a fraction of the HD population. It is estimated that about two-thirds of the patient population with HD would be eligible for the two allele-specific ASOs under clinical trials [71]. PRECISION-HD1 (WVE-120101) and PRECISION-HD2 (WVE-120102) are phase Ib/IIa RCTs currently underway in North America and Europe to determine the safety, tolerability, pharmacokinetics, and pharmacodynamics of single and multiple ascending doses of WVE-120101 and WVE-120102 [72, 73]. Preliminary results of the PRECISION-HD2 study do not raise any immediate safety concerns and report a mean reduction of 12.4% in CSF mHTT across all intervention arms compared with

placebo [59], which led to the addition of a higher dose arm in both studies. The results of these studies are expected by the end of 2020, and a phase III study is planned.

The intrathecal route of administration of ASOs is associated with a variable brain regional distribution and target engagement. Animal studies have suggested that the administration of IONIS/Roche HTTRx is associated with ~ 50% reduction of mHTT in the cortex and ~ 15 to 20% in the caudate nucleus [74]. The clinical effects of this imbalanced brain distribution are not yet fully known. The preferential targeting of cortical areas and a potential more significant rescue of cortical function may result that the disease-modifying effect of an ASO may result in a different HD phenotype, with more motor symptoms and less behavioral/cognitive symptoms [75].

The repeated administration of ASOs may be a challenge for future usage of this agent in clinical practice. Based on preclinical data [65] and modelling of data from IONIS-HTTRx study [58], the initially tested monthly injections in IONIS-HTTRx are now done every 2 to 4 months in GENERATION-HD1 study. The lesser frequency of administration assumes that the associated mean reduction in the levels of mHTT is sufficient to render a clinical effect. One of the mitigating strategies for the reduced CNS permeability of ASOs is the use of peptide conjugates that may allow for a wide CNS distribution with an intravenous administration [76, 77]. The preliminary testing for these next-generation ASOs has started in other neurological disorders such as spinal muscular atrophy [78], but not in HD.

RNA Interference-Based Strategies RNAi strategies target the evolutionarily conserved process of mRNA degradation by small noncoding RNAs [79, 80], leading to translational suppression and reduction of corresponding protein levels. Compared with ASOs, RNAi has a more downstream site of action acting on spliced mRNA in the cytosol. Broadly, RNAi strategies include small-interfering RNA (siRNA), short-hairpin RNA (shRNA), and cloned artificial microRNA (miRNA) [79] that bind to the mRNA of the target gene leading to blockage of translation or an early degradation of the transcript [79].

The main challenge with RNAi strategies is the reduced CNS permeability and cell transduction requiring the use of enhanced delivery methods through chemical modification, liposome formulation, nanoparticles, and viral vectors [79]. The use of viral vectors has been favored in HD. It requires an intracranial injection to enable the stable expression of the RNAi compound in a larger number of cells after a single dose [81, 82]. An adeno-associated virus (AAV) has been used more commonly due to strong and stable gene expression, low immunogenicity, nonpathogenicity, and inability to replicate [79]. These agents may provide long-term mHTT silencing after a single intracranial injection but also raise the concern of irreversible adverse effects. In this context, off-target effects are of greater concern as binding to mRNA sequences in unrelated genes may lead to the down-regulation of proteins other than HTT [83].

In HD, the delivery of various mHTT-targeting RNAi strategies into the striatum, putamen, or cerebral ventricles was associated with the reduction of mHTT aggregation and improvement in the experimental HD phenotype and brain pathology [79, 84, 85]. Therapeutic development is at a preclinical stage for almost all RNAi-based strategies (Table 2). The exception is the nonallele-specific miRNA AMT-130 coupled to an AAV5 vector currently being tested in a first-in-human safety sham-controlled randomized trial in early HD (NCT04120493). AMT-130 uses an MRI-guided convention-enhanced delivery system for a single bilateral caudate and putaminal administration. This study will evaluate the temporal profile of AMT-130 concentration in the brain, as well as CSF levels of DNA and miRNA expression [86].

Another compound, the AAV-delivered nonallele-specific RNAi VY-HTT01, has shown the ability to lower HTT mRNA after intracranial administration in nonhuman primates with good tolerance [87]. In a recent study, MRI-guided delivery of VY-HTT01 into the putamen and thalamus resulted in a good distribution with a dose-dependent, robust, and durable suppression of HTT mRNA and protein [88]. There are plans for a clinical trial with VY-HTT01 in the near future.
Vector-associated RNAi strategies raise challenges such as the associated surgical risks of an intracranial route of administration [89] and the limited tissue distribution of a vector-based delivery [90] which, in turn, leads to the need to determine the ideal anatomical site(s) and the optimal number of injections. The development of a viral vector able to cross the blood-brain barrier (BBB) is crucial to overcome these challenges. A RNAi strategy with a systemic administration is appealing. For example, a mutant HTT-specific RNAi coupled with an AAV9 [91] was associated with a reduction of mHTT expression in multiple brain regions and peripheral tissues following a peripheral intravenous injection in mice [92]. This approach is still in its infancy and requires extensive preclinical evaluation.

Small Molecules Targeting RNA An orally bioavailable small molecule that can cross the BBB and modulate the splicing of HTT precursor mRNA is an attractive disease-modifying strategy in HD. Splicing modulators have been shown to reduce HTT levels in HD patient-derived skin cells and neurons, and lead to a 50% reduction of CSF HTT in two fully humanized mouse HD models [93]. There are plans to conduct first-in-human trials by independent programs. (Table 2).

DNA-Based Approaches

DNA-based approaches include the inhibition of gene transcription or engineering of the HTT gene through genome editing. DNA-based approaches require the ability to bind to DNA in a specific manner and the action of nucleases, epigenetic modulators, or transcription factors [61]. Zinc-finger protein (ZFP), transcription activator-like effector (TALE), and CRIPSR/Cas9

system may have applicability to HD [61]. However, very few studies have been conducted so far (Table 2).

Zinc-Finger Protein ZFPs are engineered to target specifically the expanded CAG repeat of the HTT gene and can be coupled to transcription repressor or a nuclease effector domain to cleave DNA [94]. In HD, the ZFPs have been used as transcription repressors. Preclinical data show that ZFPs can reduce mHTT levels, HTT protein aggregates and reverse an HD-like behavioural phenotype in a mice model [53]. Similar findings were reported in patient fibroblasts, stem-cell-derived human neurons with high selectivity for the mutated HTT gene [95]. This study is part of an ongoing therapeutic development pipeline [52] that has not reached a clinical phase. As with RNAi strategies, the therapeutic delivery of ZFPs requires a viral vector and an intracranial administration. Another potential limitation of ZFPs therapeutics is the production of non-native proteins that can trigger inflammatory and immune reactions [96].

Transcription Activator-Like Effector TALEs are similar to ZFPs in that they bind to a target DNA sequence and can be coupled with transcription repressors or a nuclease. In contrast with ZFPs, the TALE DNA recognition domain is based on a sequence of amino acid repeats that binds to a specific nucleotide sequence [97]. So far, there is a single proof-of-concept preclinical study conducted in HD-patient derived fibroblasts selective decrease in mHTT expression and aggregation with TALEs [98], and there are no clinical studies or active drug development in the pipeline.

CRISPR/Cas9 System The CRISPR/Cas9 system is a gene-editing strategy that involves the highly specific identification of a double-stranded DNA sequence via the CRISPR system followed by an RNA-guided nuclease (Cas9 protein) that causes the breakage and excision of the DNA sequence [97]. For gene-replacement approaches applicable to HD, there is a need for a protospacer adjacent motif sequence that allows a specific recognition site in SNP alleles of the mutated HTT gene [99, 100]. Conceptually, the CRISPR/Cas9 system may be used to excise the mHTT gene and replace it with the wild type allele, suppress the mutated allele through the insertion of a missense mutation, or reduce transcription of the HTT gene in a non-allele specific manner, for example, through epigenetic regulation [61]. CRISPR/Cas9 system-based approaches are at very early stages of therapeutic development, with a few proof-of-concept studies in cell cultures of HD patients demonstrating the ability of CRISPR/Cas9 system to excise the mutated allele and prevent the production of the mHTT protein [56, 57, 101].

The fact that DNA-based approaches are the most proximal therapeutic target in the mHTT pathway makes them a powerful disease-modifying strategy for HD. DNA-based approaches like the CRISPR/Cas9 system can suppress any pathological species of mHTT and theoretically modify the germline, raising ethical concerns when considering research with this approach. Currently, there is a ban on CRISPR/Cas9-related research on germline in most countries.

Potential roadblocks in the development of DNA-based approaches include the immunogenicity of bacterial proteins or of new edited genes, and off-target effects with irreversible changes in other genes that can be associated with severe side effects such as cancer [102–104]. The CRISPR/Cas9 system is conceptually more straightforward in design and delivery compared to ZFP or TALE-based approaches, but the risk of off-target effects may be higher [104].

HTT Modulation

An alternative approach to mitigate the cellular effects of mHTT is to promote the clearance or inhibit aggregation of the HTT protein. PBT2 and selisistat are examples of interventions tested in clinical trials with negative results leading to the suspension of drug development programs (Table 3).

PBT2 is an 8-hydroxyquinoline transition metal ligand acting as a cellular chaperone. Although initial preclinical studies demonstrated a reduction of aggregated HTT in a mouse model [109], the clinical development of PBT2 targeted a symptomatic effect for cognition. A phase II RCT was negative for the main composite cognitive score [16]. FDA issued a Partial Clinical Hold due safety concerns based on nonclinical data, and the clinical development of PBT2 was halted since then [110]. Selisistat is a selective silent information regulator T1 inhibitor postulated to promote clearance of mHTT [111–113]. Two double-blind RCTs were conducted to assess the safety, tolerability, and efficacy of selisistat on motor disability, cognition, and functional capacity [105, 106]. The first exploratory study had only a 14-day treatment period, whereas the second was a 12-week study [105, 106]. There were no clinically relevant changes in the UHDRS, and aside from a reversible increase in liver function tests, no other safety concerns were documented. Changes in peripheral soluble mHTT were evaluated in the 12-week study that did not result in a consistent and significant finding [106].

Immunomodulation (Table 3)

In recent years, there was a growing interest in the role of aberrant immune response and other inflammatory mechanisms in the underlying pathogenesis of HD secondary to the presence of mHTT protein [114–119], leading to further neurodegeneration. Compounds with potential immunomodulating effects have been considered for disease modification in HD. Laquinimod and semaphorin 4AD (SEMA4D) are two recent examples. Laquinimod is an oral synthetic derivative of linomide repurposed from multiple sclerosis. Laquinimod was evaluated in a phase II placebo-controlled RCT (LEGATO-HD) study, which was negative for a change in the total motor score of the

Table 3 Clinical development of other therapies for disease modification in HD according to the proposed mechanism of action. (HTT-based approaches were excluded)

Compound	Mechanism of action	Name of the study	Registration ID (last date of update)	Study phase	Results
Huntingtin protein homeostasis					
PBT2	Metal-protein attenuating compound	Reach2HD	NCT01590888 (July 2016)	II	Completed Negative for efficacy [16]
Selisistat	Sirtuin-1 inhibition	Paddington –	NCT01485952 (November 2015) NCT01521585 (November 2015)	I II	Completed Negative for efficacy [105, 106]
Immunomodulation					
Semaphorin 4AD	Monoclonal antibody	SIGNAL	NCT02481674 (May 2020)	II	Ongoing Not recruiting
Laquinimod	Nf-kb inhibition Cytokine release	LEGATO-HD	NCT02215616 (May 2020)	II	Completed Negative for efficacy [107]
Other					
PF-02545920	Phosphodiesterase 10A inhibition	APACHE Amaryllis	NCT01806896 (December 2017) NCT02197130 (December 2017)	II	Completed Negative for efficacy [11, 12]
Nilotinib	Bcr-Abl tyrosine kinase inhibitor	Tasigna HD	NCT03764215 (February 2020)	Ib	Ongoing Recruiting
Cysteamine	Multiple mechanisms	CYST-HD	NCT02101957 (April 2014)	II/III	Completed Negative for efficacy [108]
SBT-20	Mitochondrial function	CHALLENGE-HD	EUCTR2016-003730-25-NL (February 2018)	Ia/II	Ongoing Not recruiting
Fenofibrate	Transcriptional co-activator (PGC-1α)	–	NCT03515213 (March 2019)	II	Ongoing Not recruiting
Resveratrol	Sirtuin-1, PGC-1α modulator	–	NCT02336633 (February 2020)	–	Completed No results in public domain

UHDRS, despite the reduced rate of caudate atrophy and whole-brain atrophy in the laquinimod arm [107]. SEMA4D is a transmembrane signalling protein that interacts with neuroinflammation processes and leads to activation of microglia and disruption of BBB [120, 121]. A monoclonal antibody to SEMA4D (VX15/2503) is currently being evaluated in the SIGNAL trial, a phase II RCT aiming to assess the effect on delaying the onset of clinical HD or the progression of clinical symptoms and signs in early HD and at a late prodromal stage [122]. Preliminary trial data suggest that VX15/2503 may have a positive effect on imaging outcomes with a lesser reduction of atrophy and metabolic activity in the brain [123]. Results of clinical outcomes are yet to be known.

Considerations for Disease-Modifying Therapies in HD

The advent of therapies targeting proximal pathways of HD biology is promising. Regardless of the outcome of the GENERATION-HD1 trial and potential identification (or not) of the first disease-modifying therapy in HD, it is inevitable that other human clinical trials for disease modification in HD will be conducted to find more effective treatments, with less invasive routes of administration.

An important question related to HTT-lowering therapies is the requirement for allele specificity or not, mostly in terms of their safety. Data gathered so far is inconclusive regarding allele-specific approaches being potentially safer as they only target the mHTT. While a knockout mouse model for normal HTT does not survive past embryonic development [124, 125], and the absence of normal HTT in an HD preclinical model has been associated with a worsening phenotype [126, 127], the partial suppression of HTT seems to be safe in a rhesus macaque model [128]. The short-term safety data from human studies of nonallele-specific approaches did not raise relevant issues [58]. The observed reduction of around 40% of CSF HTT levels in IONIS-HTTRx study [58] is less than the 50–75% threshold of safety in preclinical models [129]. Nevertheless, the long-term safety of nonallele-specific therapies needs to be determined. Allele specificity dictates the development and implementation of novel HTT-lowering therapies. Allele-specific approaches have a higher cost associated with the independent development of different compounds targeting different groups of people with HD and the need for regulatory approval of each agent compared to the nonallele-specific approach. Nonallele-specific approaches

have the advantage of potentially being applicable to all patients with HD [130].

A significant challenge to a novel disease-modifying therapy in HD is the feasibility of its implementation and associated costs. For example, the need for repeated intrathecal administration of ASOs [131] is deemed to put pressure on existing health care systems. Significant investment will be necessary for the development of clinical expertise and infrastructure for the long-term administration of a treatment like ASOs. The societal cost of the treatment is not established. As an example, the cost of nusinersen, an ASO approved for the treatment of spinal muscular atrophy, amounts to approximately USD $72,000–130,000 in the first year of treatment and USD $36,000–65,000 annually thereafter [132].

The possibility to conduct a disease-modifying trial in subjects at a premanifest/prodromal stage will begin to be seriously considered to intervene earlier in the disease when neurodegeneration is less and rescue potential larger. Although the ease with which subjects can be diagnosed before the onset of clinical symptoms places HD as an ideal model of neurodegenerative disease to develop disease-modifying therapies, trials in premanifest or prodromal stages raise tremendous challenges for study design. One crucial question is the duration of the study. HD is a slowly progressive disease, and the ability to identify a significant therapeutic effect could mean a very long trial with prohibitive costs and considerable attrition risk. Strategies to optimize such design include small proof-of-concept studies to identify the interventions with a better target engagement for disease modification and enrichment strategies to include those subjects closer to phenoconversion. The latter implies a staging system of the natural history of HD using both clinical and biomarker data as explicit and feasible criteria to define HD stages [133]. In turn, these stages could be used to define which populations to include in a trial and to treat in the future, if a disease-modifying therapy is approved for premanifest/prodromal HD. Finally, the ability to monitor disease progression beyond currently available clinical outcomes is necessary as individuals in a prodromal phase have minimal clinical features not captured by current clinical rating scales. The HD field is making significant efforts to address these challenges, with the development of biomarkers and clinical rating scales to capture the very early clinical changes in HD. Many of these efforts are being coordinated by the HD-Regulatory Science Consortium (Critical Path Institute/CHDI Foundation) that congregate academia, industry, and regulatory agencies with the goals of enhancing the regulatory path for emerging therapies for HD [133]. The Functional Rating Scale 2.0 and Huntington disease cognitive assessment battery (HD-CAB) are examples of new clinical outcome measures developed for use in clinical trials to capture changes in premanifest and early-manifest HD [133]. Also, a series of nonclinical candidate biomarkers have been put forward to aid therapeutic development. Imaging biomarkers include MRI-based caudate, white matter, whole-brain volumes, white matter integrity measured by DTI-MRI, nuclear imaging with PET using tracers for mHTT or PDE10, and quantification of myoinositol, NAA through MR spectroscopy [133]. Wet biomarkers include the quantification of CSF mHTT, total HTT, neurofilament light protein (NfL), and plasma NfL. Among these, volumetric-based imaging of the caudate/putamen consistently shows the ability to track disease progression many years before motor phenoconversion [9, 134–136] and could be used as enrichment criteria or to track disease progression. The group of biomarkers tracking mHTT is very appealing in the context of HTT-lowering clinical trials [137]. CSF mHTT was already used in the IONIS-HTTRx trial [58] and was the result of the availability of a novel immunoassay validated by regulatory standards for its ability to measure mHTT in picomolar concentrations [138]. A series of clinical correlation studies showed that CSF mHTT level was higher in manifest HD compared with premanifest mutation carriers and an association with measures of clinical severity [139], clinical disease progression, and the 5-year onset probability [140]. Although CSF mHTT is not a direct measure of brain mHTT levels, data from animal studies provide evidence that CSF mHTT may relate to mHTT being released from dying neurons [139]. Another approach to measure mHTT in HD is through PET imaging. The PET radioligand CHDI-00485180 for mHTT is under evaluation in both manifest and premanifest HD [141]. An mHTT PET could help to document the regional differences in the effect of ASOs or other HTT-lowering agents at a proof-of-concept stage of clinical development and as exploratory efficacy outcomes.

More recently, neuronal cytoskeleton components such as NfL and tau were proposed as markers of neurodegeneration in HD [142, 143]. For NfL, the validity of using plasma has been explored, which could represent a less invasive and safer procedure compared with a CSF-sourced biomarker. Plasma NfL levels showed a good correlation with CSF levels [137] and a fair correlation with brain atrophy, cognitive decline rates, and phenoconversion [144]. An observational study (HDClarity, clinicaltrials.gov NCT02855476) is currently underway to aid in the development of wet biomarkers in HD populations.

Final Remarks

The advances in the understanding of HD pathogenesis led to the current therapeutic landscape in which different strategies aim to lower the levels of the pathogenic mHTT protein and its biological effects. ASOs are already in a phase of clinical trials, and the ongoing trial GENERATION-HD1 may dramatically change the management of HD in the near future. For the vast majority of other HTT-lowering therapies, the

current preclinical development may be followed by human clinical trials. Regardless of the results of ongoing clinical trials, the implementation of more robust molecular and imaging biomarkers, and more sensitive clinical scales are instrumental for the next clinical trials in HD. It is expected that not only early HD patients but also a prodromal HD population will take part in these trials.

Required Author Forms Disclosure forms provided by the authors are available with the online version of this article.

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