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Huntington's Disease Clinical Trials Corner: June 2019

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Abstract. In this edition of the Huntington's Disease Clinical Trials Corner we expand on the HD-DBS and on the TRIHEP3 trials, and we list all currently registered and ongoing clinical trials in Huntington's disease.

Keywords: Huntington disease, clinical trials

INTRODUCTION

The Huntington's Disease Clinical Trials Corner is a regular section devoted to highlighting ongoing and recently completed clinical trials in Huntington's disease (HD). Clinical trials previously reviewed by the Huntington's Disease Clinical Trials Corner are listed in Table 1.

In this edition, we highlight the HD-DBS trial (NCT02535884)(1), and the TRIHEP3 trial (NCT02453061)(2). We tabulate all currently registered and ongoing clinical trials in Tables 2 to 4. For further details on the methodology used, please refer to the first edition of Huntington's Disease Clinical Trials Corner(3).

If you would like to draw attention to specific trials, please feel free to email us at: f.rodrigues@ucl.ac.uk and e.wild@ucl.ac.uk.

In addition to the above, the published report of the IONIS-HTT_{Rx} trial (NCT02519036) is worthy of mention. The paper reports that monthly intrathecal IONIS-HTT_{Rx}/RG6042 – an antisense oligonucleotide that signals wild-type and mutant huntingtin pre-mRNA to be degraded by RNase H1 – was safe and well-tolerated, and produced dose-dependent reductions in cerebrospinal fluid mutant huntingtin in early HD patients (4). This is an interesting signal but caution should be exercised as to whether this reduction translates into a clinically significant benefit for people with HD. Further investigation into the effects of this drug are expected from the currently ongoing phase 3 GENERATION-HD1 trial (NCT03761849)(5) and associated studies (6–10). These studies will help us better characterize the safety profile of this compound, define the most efficient posology, and understand if it is associated with a clinically relevant benefit, and towards which disease domain.

ONGOING CLINICAL TRIALS

A list of all ongoing clinical trials is given in Tables 2–4.

HD-DBS (NCT02535884)

Study title

Deep Brain Stimulation (DBS) of the Globus Pallidus (GP) in Huntington's Disease (HD) (HD-DBS)(1).

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Table 1
Clinical trials previously reviewed by the Huntington's Disease Clinical Trials Corner

	Trial name	Intervention	Edition
NCT02519036	IONIS-HTTRx	IONIS-HTT_{Rx}*	September 2017(3)
NCT02215616	LEGATO-HD	Laquinimod	
NCT02197130	Amaryllis	PF-02545920	
NCT02006472	PRIDE-HD	Pridopidine	
NCT03225833	PRECISION-HD1	WVE-120101	February 2018(28)
NCT03225846	PRECISION-HD2	WVE-120102	
NCT01795859	FIRST-HD	Deutetrabenazine	
NCT02481674	SIGNAL	VX15/2503	August 2018(29)
NCT00712426	CREST-E	Creatine	
NCT03761849	GENERATION-HD1	RG6042*	January 2019(30)
NCT03344601	PACE-HD	Physical activity	
NCT02535884	HD-DBS	Deep brain stimulation	June 2019
NCT02453061	TRIHEP3	Triheptanoin	

*IONIS-HTT_{Rx} and RG6042 refer to the same molecule.

Intervention

DBS of the GP (11) with Medtronic ACTIVA® PC neurostimulator (Model 37601).

Description

The HD-DBS trial, sponsored by Heinrich-Heine University, aims to evaluate the efficacy and safety of pallidal DBS in adults (18 or more years of age) with manifest HD (i.e. clinically symptomatic and genetically confirmed [CAG $\geq$36]) and moderate disease stage (defined by the investigators as an Unified Huntington's Disease Rating Scale [UHDRS] total motor score [TMS] $\geq$30), chorea (UHDRS chorea score $\geq$10) and a Mattis Dementia Rating Scale $\geq$120, comparing with sham stimulation, for motor function.

People with juvenile or predominantly bradykinetic forms of the disease, postural instability, unstable medication in the 6 weeks previous to inclusion, unstable medical or psychiatric comorbidities, coagulopathies and/or increased risk of haemorrhage, implanted pacemaker or defibrillator, pregnant or breast-feeding are not eligible for this study.

This trial is an international, multi-centre, randomized, sham-controlled, double-blind, parallel study. It has 2 study arms: the stimulation group, where participants have stimulation turned on immediately after implantation of the stimulator; and the sham stimulation group, where participants will have a stimulator implanted but it will not be switched on. The study lasts 12 weeks, and after that period all participants' stimulators will be turned on.

The trial has already started recruitment, and has a recruitment target of 50 participants, over 4 countries (Austria, France, Germany and Switzerland) and 12 sites.

The primary outcome is the UHDRS TMS at 12 weeks, measured as the difference in the mean change from baseline between the stimulation arm and the sham-stimulation arm. The secondary outcomes include the UHDRS chorea score and the bradykinesia items, the Burke-Fahn-Marsden Dystonia Rating Scale, the Q-Motor choreomotography task, the Mattis Dementia Rating Scale, the Verbal Fluency Test, the Symbol Digits Modalities Test, the Stroop Test, the Hospital Anxiety and Depression Scales and the Snaith Irritability Scale, the Problem Behaviours Assessment Short Form, the Short Form 36 Health Survey, the Clinical Global Impression Scale, and safety.

Sponsors/funders

Heinrich-Heine University, KKS Netzwerk, Medtronic, the George Huntington Institute, EHDN and CHDI Foundation.

Comments

DBS is a relatively well-studied intervention for some manifestations of Parkinson's disease, tremor and dystonia. DBS involves the surgical implantation of electrical electrodes in the deep brain structures, connected via a wire to an implantable pulse generator (i.e. stimulator) usually positioned subcutaneously in the pectoral region. Although the precise mechanisms of action are still not completely understood, this intervention is aimed at interrupting certain neuronal circuits.

In Parkinson's disease DBS is frequently used to minimize levodopa-induced dyskinesia, which has a similar phenomenology to chorea in HD, but a different aetiology. This is accomplished by bet-

Table 2
Ongoing pharmacological clinical trials registered at the World Health Organization (WHO) International Clinical Trials Research Platform (ICTRP) for people with Huntington's disease (HD)

Registration ID	Trial name	Intervention	Mechanism of Action	Population	Comparison	Main outcome	Study design	Estimated Enrolment	Sponsor	Location
NCT03854019*	–	Dextromethorphan/ quinidine	Morphinan/class I antiarrhythmic agent	HD with irritability	Placebo	Clinical efficacy at 6 and 13 weeks	Randomized, double-blind, placebo-controlled, cross-over trial	22	University of Texas Health Science Center, Cures Within Reach	USA (single centre)
NCT03842969*	GEN-EXTEND	RG6042	Allele- nonselective antisense oligonucleotide	HD	None	Safety and tolerability at up to 5 years	Open-label extension	950	Hoffmann-La Roche	USA, Canada, Europe (multi centre)
NCT03761849	GENERATION-HD1	RG6042	Allele- nonselective antisense oligonucleotide	HD	Placebo	Clinical efficacy at 101 weeks	Randomized, double-blind, placebo-controlled, parallel trial	660	Hoffmann-La Roche	USA, Canada, Europe (multi centre)
NCT03787758	–	SAGE-718	NMDA positive allosteric modulator	HD	Placebo	Safety at 21 days	Randomized, double-blind, placebo-controlled, multiple ascending dose trial	10	Sage Therapeutics	N/S
NCT03575676	–	SOM3355	VMAT2 inhibitor and β1 antagonist	Early and moderate HD with chorea	Placebo	Chorea at 6 months	Randomized, double-blind, placebo-controlled, cross-over trial	30	SOM Biotech SL	Spain (multi centre)
NCT03515213	–	Fenofibrate	PPARα agonist	HD	Placebo	Pharmacodynamics at 6 months	Randomized, double-blind, placebo-controlled, parallel trial	20	University of California, Irvine	USA (single centre)
NCT03764215	Tasigna HD	Nilotinib	Selective Bcr-Abl tyrosine kinase inihbitor	HD	None	Safety, tolerability and pharmaco-dynamics at 3 months	Open label, multiple ascending dose	20	Georgetown University	USA (single centre)
NCT03342053	IONIS-HTT_{RX} OLE	ISIS 443139	Allele- nonselective antisense oligonucleotide	HD	None	Safety and tolerability at 74 weeks	Open label extension	46	Ionis Pharmaceuticals Inc.	Canada, Germany and UK (multi-centre)
NCT03225833	PRECISION-HD1	WVE-120102	Allele-selective antisense oligonucleotide	HD	Placebo	Safety and tolerability at 1 and 120 days	Randomized, double-blind, placebo-controlled, combined single ascending dose/multiple ascending dose trial	48	Wave Life Sciences Ltd.	Canada and Poland (multi-centre)
NCT03225846	PRECISION-HD2	WVE-120102	Allele-selective antisense oligonucleotide	HD	Placebo	Safety and tolerability at 1 and 120 days	Randomized, double-blind, placebo-controlled, combined single ascending dose/multiple ascending dose trial	48	Wave Life Sciences Ltd.	Canada and Poland (multi-centre)

(*Continued*)

Table 2
(*Continued*)

Registration ID	Trial name	Intervention	Mechanism of Action	Population	Comparison	Main outcome	Study design	Estimated Enrolment	Sponsor	Location
NCT02453061	TRIHEP 3	Triheptanoin	Anaplerotic therapy	HD	Safflower oil	Pharmacodynamic efficacy at 6 months	Randomized, double-blind, controlled, parallel trial	100	Institut National de la Santé Et de la Recherche Médicale, Ultragenyx Pharmaceutical Inc	France, Netherlands (multi centre)
NCT02509793	–	Tetrabenazine	VMAT2 inhibitor	HD with impulsivity	None	Cognitive and behavioural effects at 8 weeks	Single group, open-label trial	20	University of Texas Health Science Center, and H. Lundbeck A/S	USA (single centre)
NCT02481674	SIGNAL	VX15/2503	Anti-semaphorin 4D monoclonal antibody	Late premanifest or early HD	Placebo	Safety and tolerability at 15 and 21 months	Randomized, double-blind, placebo-controlled, parallel trial	240	Vaccinex Inc., Huntington Study Group	USA (multi centre)
NCT02336633	REVHD	Resveratrol	Dietary supplement	HD	Placebo	Neuroimaging biomarkers at 1 year	Randomized, double-blind, placebo-controlled, parallel trial	102	Assistance Publique - Hôpitaux de Paris	France (multi centre)
EUCTR2013-002545-10-SE	OSU6162Open1309	(-)-OSU616	Monoaminergic stabilizer	HD, PD, brain trauma, stroke, myalgic encephalomyelitis and narcolepsy	None	Safety at 3, 6 and 12 months	Single group, open-label trial	240	A. Carlsson Research AB	Sweden (multi centre)
NCT00514774	UDCA-HD	Ursodiol	Bile acid	HD	Placebo	Safety, tolerability and pharma-cokinetics at 35 days	Randomized, double-blind, placebo-controlled, parallel trial	21	Oregon Health and Science University, Huntington Study Group, Huntington Society of Canada	N/S

N/S, not specified; PD, Parkinson's disease; VMAT2, Vesicular Monoamine Transporter 2. Note: IONIS-HTT$_{Rx}$, ISIS 443139 and RG6042 refer to the same molecule. New trials since the last Clinical Trials Corner are indicated by*.

Table 3
Ongoing invasive non-pharmacological clinical trials registered at the World Health Organization (WHO) International Clinical Trials Research Platform (ICTRP) for people with Huntington's disease (HD)

Registration ID	Trial name	Intervention	Mechanism of Action	Population	Comparison	Main outcome	Study design	Esimated Enrolment	Sponsor	Location
ISRCTN52651778	TRIDENT	Foetal stem cell transplant	Stem cell therapy	Early stage HD	Usal care	Safety at 4 weeks	Randomized, open label, controlled, parallel trial	30	Cardiff University	UK (single centre)
NCT02728115	SAVE-DH	Cellavita	Stem cell therapy	HD	None	Safety at 5 years	Non-randomized, open label, uncontrolled, parallel trial	6	Azidus Brasil	Brazil (single centre)
NCT03252535	ADORE-HD	Cellavita	Stem cell therapy	HD	Placebo	Efficacy at 120 days	Randomized, double-blind, placebo-controlled, parallel trial	35	Azidus Brasil	Brazil (single centre)
NCT03297177	–	Autologous stem/stromal cells	Autologous stem/stromal cell injection	HD, AD, PD, CBD, MS	None	Safety at 5 years	Single group, open-label trial	300	Healeon Medical Inc, Global Alliance for Regenerative Medicine, Regeneris Medical	USA and Honduras (multi-centre)
NCT02535884	HD-DBS	GP DBS	Deep brain stimulation	Moderate HD with chorea	Sham intervention	Efficacy at 12 months	Randomized, double-blind, sham-controlled, parallel trial	50	Heinrich-Heine University, KKS Netzwerk, Medtronic, The George Institute, EHDN, CHDI Foundation, Inc.	Austria, France Germany, Switzerland (multi centre)
NCT01834053	BMACHC	Bone Marrow Derived MNC transplant	Bone marrow transplant	HD with chorea	None	Cognitive and behavioural effects at 6 months	Single group, open-label trial	50	Chaitanya Hospital, Pune	India (single centre)
NCT02263430	–	GP DBS	Deep brain stimulation	HD with chorea	Sham stimulation	Efficacy at 12 months	Randomized, double-blind, placebo-controlled, parallel trial	8	Beijing Pins Medical Co., Ltd, Beijing Tiantan Hospital	China (single centre)
NCT02252380	–	Magnetic Resonance Guided Focused Ultrasound	Extracranial stereotactic radioablation	HD, ET, HT, PD, WD, dystonia, TD, or orofacial dyskinesias	None	Adverse events after the procedure	Single group, open-label trial	10	InSightec	Canada (single centre)

AD, Alzheimer's disease, CBD; Corticobasal Degeneration; DBS, deep brain stimulation; ET, Essential Tremor; GP, Globus pallidus; HT, Holmes Tremor; MNC, mononuclear cells; MS, Multiple Sclerosis; PD, Parkinson's disease; TD, Tardive dyskinesia; WD, Wilson's disease.

Table 4
Ongoing non-invasive non-pharmacological clinical trials registered at the World Health Organization (WHO) International Clinical Trials Research Platform (ICTRP) for people with Huntington's disease (HD)

Registration ID	Trial name	Intervention	Mechanism of Action	Population	Comparison	Main outcome	Study design	Esimated Enrolment	Sponsor	Location
ACTRN12618001717246	–	Multidisciplinary therapy program	Exercise, cognitive training, lifestyle guidance and social activities	PremanifestHD	Standard of care	Feasability and safety	Clustered, non-randomized, open label, parallel trial	40	Edith Cowan University, Deakin University and Lotterywest	Australia (two centres)
NCT03417583	–	Neuropsychiatric treatment protocol	Multidisciplinary intervention	HD with neuropsychiatric symptoms	Standard of care	Change in quality of life at 18 months	Non-randomized, assessor-blinded, parallel trial	100	Vanderbilt University Medical Center and Teva Pharmaceuticals USA	USA (single centre)
CTRI/2018/01/011359	–	Repetitive transcranial magnetic stimulation	Transcranial magnetic stimulation	Early to moderate HD and PD	Sham stimulation	Efficacy at 5 days	Randomized, single-blind, placebo-controlled, parallel trial	40	Vinay Goyal	India (single centre)
NCT03344601	PACE-HD	Supported structured aerobic exercise training program	Physiotherapy	HD	Activity as usual	Data completeness, recruitment, retention, safety, adherence, fidelity and acceptability at 12 months	Nested open-label, randomized controlled parallel trial	120	Cardiff University and CHDI Foundation, Inc	Germany, Spain and USA (multi centre)
ACTRN12617001269325	–	Swallowing skill training	Speech and language therapy	HD and ALS	None	Swallowing function and quality of life at 2 weeks	Single group, open-label trial	54	University of Canterbury	New Zealand (single centre)
NCT02216474	–	tDCS	Transcranial magnetic stimulation	HD or Tourette Syndrome	Sham stimulation	Efficacy at 2 weeks	Randomized, double-blind, placebo-controlled, cross-over trial	100	Birmingham and Solihull Mental Health NHS Foundation Trust, University of Birmingham	UK (single centre)

AD, Alzheimer's disease; ALS, Amyotrophic Lateral Sclerosis; ET, Essential Tremor; HT, Holmes Tremor; MS, Multiple Sclerosis; PD, Parkinson's disease; TD, Tardive dyskinesia.

ter controlling the cardinal features of PD, hence reducing the levodopa dose equivalents. There is still uncertainty about whether there is a direct effect of DBS over dyskinesia. In HD, chorea is thought to be caused by the loss of striatal projections to the indirect basal ganglia pathway and consequent thalamic overactivity (11), and although there is a shortage of good-quality evidence, some pilot studies have shown interesting preliminary results when manipulating these circuits with DBS in HD (12, 13).

The scarcity of data so far accumulated precludes drawing conclusions on the safety and efficacy profile of this intervention in HD, but it seems sensible to assume that this population may be susceptible to the same intervention-related adverse events as other tested populations. Disease-specific side effects may be more difficult to predict.

Only large well-controlled prospective controlled studies will allow us to fully understand the efficacy and safety profile of DBS in HD.

TRIHEP3 (NCT02453061)

Study title

A Comparative Phase 2 Study Assessing the Efficacy of Triheptanoin, an Anaplerotic Therapy in Huntington's Disease (TRIHEP3)(2).

Intervention

Triheptanoin oil 1 g/kg/day (14).

Description

The TRIHEP3 trial, sponsored by the Institut National de la Santé et de la Recherche Médicale and Ultragenyx Pharmaceutical Inc., aims to evaluate the effects of daily triheptanoin in adults ($\geq$18 years of age) with genetically confirmed manifest HD (i.e. UHDRS TMS between 5 and 40), compared with daily safflower oil. People with a BMI <18 or >30, hypersensitivity to triheptanoin, major co-morbidities, history of severe head injury, pregnant or breastfeeding, or on tetrabenazine are not eligible.

TRIHEP3 is an international, multi-centre, randomized, double-blind, controlled, parallel phase 2 trial. It has 2 study arms: the active group, where participants receive triheptanoin oil 1 g/kg/day for 12 months; and the comparator group, where participants receive safflower oil 1 g/kg/day for 6 months and triheptanoin oil 1 g/kg/day for the following 6 months.

The study lasts 12 months, the first half over double-blinded conditions, and the second half as an open-label extension. Recruitment is currently closed and the study is being performed at one centre in France and one centre in the Netherlands. One hundred participants were recruited.

The primary outcomes are pharmacodynamics neuroimaging markers at 3 and 6 months - ^{31}P-MRS and volumetric MRI. Secondary outcomes include the UHDRS, comprising the motor, functional and cognitive components, the Problem Behaviours Assessment Short Form, the Short Form 36 Health Survey, adverse events, tolerance and other neuroimaging biomarkers.

Sponsors/funders

Institut National de la Santé et de la Recherche Médicale and Ultragenyx Pharmaceutical Inc.

Comments

Albeit with a low success rate (15), several dietary nutrients with possible effects over metabolic processes have been tested in HD over the years, including d-α-tocopherol (16), idebenone (17), coenzyme Q10 (18), ethyl-eicosapentaenoate (19–21), and creatine (22–24).

Triheptanoin is an odd-chain triglyceride with anaplerotic properties (i.e. it replenishes biochemical cycles with intermediate metabolites), providing the Krebs cycle with both acetyl-CoA and propionyl-CoA. So far, triheptanoin has been tested for several disorders of the brain metabolism, including pyruvate decarboxylase deficiency, and GLUT1 deficiency where a significant symptomatic effect was demonstrated in a small open-label study (25).

In HD, several lines of evidence support the existence of a dysfunction of the energy metabolism, including the Krebs cycle, oxidative phosphorylation and glycolysis. Two small open-label studies in HD showed that triheptanoin may have the potential to bring peripheral (26) and central nervous system metabolic biomarkers (27) to levels observed in healthy controls. They also anticipate triheptanoin to be well tolerated (26, 27), and overall the cumulative evidence suggests a good safety profile for doses between 1 to 2.5 g/kg/day(14).

The TRIHEP3 trial will be completed by the end of 2019 and the results are expected in mid-2020.

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CONFLICTS OF INTEREST

FBR and EJW were sub-investigators on LEGA TO-HD (NCT02215616), IONIS HTT_{Rx} (NCT0251 9036) and IONIS HTT_{Rx} OLE (NCT03342053), and are sub-investigators on the Roche GENERATION-HD (NCT03761849), Roche Natural History Study (NCT03664804) and Roche GEN-EXTEND (NCT03842969) trials, and EJW was a sub-investigator on the Amaryllis (NCT02197130). EJW is the chief investigator of the Roche GEN-PEAK trial (NCT04000594) and FBR is a sub-investigator. JJF was principal investigator on LEGATO-HD and on a trial of ethyl-eicosapentanoate in Huntington's disease. The authors did not make use of confidential or privileged information: all materials included in this manuscript were collected from publicly available sources. FBR has provided consultancy services to GLG. EJW has participated in scientific advisory boards with Hoffmann-La Roche Ltd, Ionis, Shire, GSK, Wave Life Sciences, PTC Therapeutics, Takeda and Mitoconix. All honoraria were paid through UCL Consultants Ltd, a wholly owned subsidiary of UCL. Their Host Institution, University College London Hospitals NHS Foundation Trust, has received funds as compensation for conducting clinical trials for Ionis Pharmaceuticals, Pfizer and Teva Pharmaceuticals. Hoffman La Roche Ltd has supported UCL with research funding for EJW. In view of the support to both regular authors from Hoffman-La Roche Ltd, JJF was invited to be a co-author to ensure the sections on the Ionis/Roche program were suitably balanced.

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