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Clinical Trials in Rare Disease: Challenges and Opportunities

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Abstract

The neuronal ceroid lipofuscinoses constitute one of many groups of rare childhood diseases for which disease-modifying treatments are non-existent. Disease-specific barriers to therapeutic success include incomplete understanding of disease pathophysiology and limitations of treatments that cannot adequately cross the blood-brain barrier to access the central nervous system. Therapeutic development in the neuronal ceroid lipofuscinoses shares many challenges with other rare diseases, such as incomplete understanding of natural history to inform trial design, need for alternatives to the randomized controlled clinical trial, requirement for more sensitive outcome measures to quantify disease, limited access to resources required to mount a clinical trial (including funding), and difficulties of recruiting a small sample to participation. Solutions to these barriers will require multicenter collaboration, partnership with patient organizations, training a new generation of researchers interested in rare diseases, and leveraging existing resources.

Keywords

Batten disease; clinical trials; lysosomal storage disease; neuronal ceroid lipofuscinosis; rare disease

Introduction

The neuronal ceroid lipofuscinoses are a group of lysosomal storage diseases characterized by intracellular accumulation of autofluorescent lipofuscin. They are unified by the broad clinical symptoms of vision loss, epilepsy, motor impairment, dementia, and shortened lifespan, but are distinguished by age at onset, clinical course, ultrastructural morphology, and genetic basis. Descriptions of each distinct clinical phenotype and underlying pathobiology have been outlined in recent reviews and by other contributors to this supplement.[1-4] At least 9 forms of neuronal ceroid lipofuscinosis are recognized, including CLN1, CLN2, CLN3, CLN4, CLN 5, CLN6, CLN7, CLN8, and CLN10.[3]

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EA wrote the first draft of the manuscript. All authors critically revised the manuscript and approved the final version of the manuscript.

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Ethical Approval
Not applicable

Current State of Treatment in the Neuronal Ceroid Lipofuscinoses

The constellation of symptoms associated with the neuronal ceroid lipofuscinoses are difficult to manage due to their complexity, ongoing evolution, and potentially long duration. In addition, the presence of dementia impacts the affected individual's ability to understand or cope with symptoms and can impact assessment of other clinical features. Behavioral problems tend to be among the most challenging symptoms. In a case series of 9 children with infantile, late-infantile, or juvenile neuronal ceroid lipofuscinosis in a hospice setting, sleep disturbance, agitation, joint stiffness, and oral secretions were reported by parents to be the most difficult symptoms to manage.[5] Advancements in supportive care have led to prolonged life expectancy, but may unintentionally prolong symptoms that negatively affect quality of life. Compounding these factors, the rarity of each of these disorders limits the clinical experience of many practitioners and contributes to the lack of evidence-base to guide clinical care.[6]

Current treatments for all of the neuronal ceroid lipofuscinoses focus on symptomatic care: antiepileptics for seizure management; physical/occupational therapy and medications to address motor impairment and movement disorders; and psychotropic medications and behavioral therapies to reduce the impact of psychiatric and behavioral problems. Special education services accommodate cognitive impairments and vision loss. Our management strategies are relatively independent of the specific neuronal ceroid lipofuscinosis diagnosis and are often incomplete in their ability to achieve symptom control.

Although the first cases were described almost 200 years ago,[7] there are still no proven disease-modifying therapy for any form of neuronal ceroid lipofuscinosis. Since 1977, there have been at least 5 completed prospective parallel group clinical trials and 19 case reports, series, or open-label studies addressing treatments for infantile, late-infantile, and juvenile neuronal ceroid lipofuscinosis (Table 1). In addition, one study used existing research-based natural history data to evaluate a specific treatment provided in a clinical, non-research setting.[8] To date, there are no reports of clinical trials for other neuronal ceroid lipofuscinoses. Of the studies completed over this 35-year time period, 13 evaluated potential disease-modifying therapies: hematopoietic stem cell transplant,[9-12] central nervous system stem cell transplantation,[13] immunomodulation,[14] polyunsaturated fatty acids,[15,16] antioxidant therapy,[17-20] and nonopioid analgesics.[8] Only 8 reported a sample of greater than 20 participants. Some initial studies were followed by separate reports of longer subject follow-up; both are included here. For some studies, large samples were acquired over prolonged periods of time. Interpretation of results from many of these studies is limited by small samples, lack of internal or historical controls, limited use of quantitative measures, and for the slowly progressing juvenile form, a relatively short period of follow-up that may be too brief to detect meaningful change.[21,22]

The relative paucity of published clinical trials and small sample sizes reflect the challenges of trial execution in rare disease and the need for therapeutic development in the neuronal ceroid lipofuscinoses. We are encouraged that a new phase of therapeutic development has begun – there are currently 5 ongoing clinical trials, all evaluating potential disease-modifying therapies. All but one of these trials plan to enroll samples of greater than 10 subjects; one is a randomized controlled trial, and 2 are parallel group trials (Table 2).[13,23-28] Ongoing preclinical research hints at potential future human investigations based on α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA) receptor antagonism,[29,30] *N*-methyl-D-aspartate receptor antagonism,[31] central nervous system-directed enzyme replacement therapy,[32] and combination therapies such as hematopoietic stem cell transplantation plus gene therapy.[33]

Challenges to Therapeutic Development in the Neuronal Ceroid Lipofuscinoses

Current research strategies mostly rely on individual therapeutic approaches for specific neuronal ceroid lipofuscinoses or small groups of neuronal ceroid lipofuscinoses based on similarities in protein characteristics.[34,35] Some approaches under exploration require attention to mutation type, such as readthrough therapy or pharmacological chaperones for nonsense or missense mutations, respectively.[36-38] These issues magnify the challenges of study design for small samples in the already rare neuronal ceroid lipofuscinoses collectively, then divided by CLN-type, and possibly further by specific mutation. It remains unclear whether a single therapy can be developed that will be valid for all neuronal ceroid lipofuscinoses.

Target-driven drug discovery is reliant upon in-depth understanding of the underlying mechanisms and pathophysiology of disease and a biological hypothesis.[39] For most neuronal ceroid lipofuscinoses, the causative gene is known, yet understanding of pathophysiology remains incomplete, posing challenges for rational therapeutic development. In the case of juvenile neuronal ceroid lipofuscinosis, isolation of the hydrophobic transmembrane CLN3 gene product remains a significant barrier.[40]

Following identification of candidate compounds, the greatest therapeutic challenges relate to crossing the blood-brain barrier to address the neurodegenerative process, be it for prevention, repair, or to slow disease progression. Enzyme replacement may be a feasible strategy for CLN1, CLN2, and CLN10, which each have a soluble enzyme defect. Intravenous enzyme replacement therapy has been a partially successful strategy for lysosomal storage disorders with visceral manifestations, including Pompe,[41] Fabry,[42] mucopolysaccharidosis I,[43] mucopolysaccharidosis II,[44] and Gaucher[45-47] diseases. However, this approach has not significantly reduced central nervous system disease impact.[48,49] In the neuronal ceroid lipofuscinoses, where central nervous system manifestations predominate, alternate delivery modes would be required. Even where intraventricular or intrathecal delivery is possible, widespread distribution is a challenge and may require multiple infusion sites in the larger human brain in comparison to murine experiments; this also holds true for viral-mediated gene therapy.[32] Data regarding central nervous system delivery of recombinant human enzyme replacement therapy in humans is lacking, and thus the long-term safety and effects are unknown. Enzyme replacement is less likely to represent a feasible strategy for CLN3, CLN5, CLN6, and CLN8, which have primary defects in transmembrane proteins.

Similar problems of crossing the blood-brain barrier are presented for cell-based therapies such as hematopoietic stem cell transplant. Cerebral implantation of human neural stem cells bypasses this concern, but again is appropriate only for neuronal ceroid lipofuscinoses that result from soluble enzyme defects. The ability to replace specific cells in the nervous system, to replace multiple cell types, or to recapitulate or integrate into complex neural networks is unclear as it relates to cell-based therapies for neurological disorders. There are limited long-term data supporting clinical ability to deliver deficient enzyme via cell-based or gene-based approaches.

Lastly, there is no expectation of reversal of the disease process with any therapy currently under exploration. There may be a critical early window for intervention before significant irreversible neurodegeneration has occurred such that early recognition or even pre-symptomatic diagnosis will become increasingly important.

Clinical Trials in Rare Diseases – Broader Challenges and Opportunities

In addition to the disease-specific complexities above, therapeutic development in the neuronal ceroid lipofuscinoses shares challenges with other lysosomal storage disorders and with rare diseases as a whole. The Orphan Drug Act defines rare diseases as disorders affecting fewer than 200 000 individuals in the United States.[50] Collectively, the more than 8000 recognized rare diseases affect almost 30 million individuals and their families in the United States.[51] Many of the concepts addressed here are common challenges to therapeutic development in rare diseases, and thus where there is success for one rare disease, there is opportunity to inform research in others.

There are several requirements for therapeutic study of human diseases: appropriate trial design and analysis to answer the research question, appropriate measurements to complement the trial design, selection of the correct sample, ethical recruitment to participation, funds to support the research, knowledgeable study staff, and adequate resources to execute the study and address regulatory concerns. In rare diseases, the limitations that studying a small population bring can transform these requirements into monumental challenges.

Trial Design

The randomized controlled trial is often considered the gold standard for establishing efficacy in a research setting.[52] This design minimizes selection bias and distributes confounders, known and unknown, between study groups. Together, randomization and blinding have the potential to limit investigator and participant bias in outcomes assessment. To use this classic clinical trial design to detect small therapeutic effects, as is often done for common diseases, is costly, time-consuming, and requires large sample sizes — all of which are less feasible in rare diseases. A small, uncontrolled trial can be an appropriate alternative for a well-understood disease with a homogenous clinical course, and where the anticipated effect size is large. Yet, in the neuronal ceroid lipofuscinoses, even as single gene disorders, there is considerable variability, even within families with multiple affected children presumably all carrying the same mutation(s) and similar modifiers.[21,22,53-55] In addition, we continue to gain knowledge of previously unrecognized aspects of disease such as cardiac conduction abnormalities in juvenile neuronal ceroid lipofuscinosis.[56]

Use of controls will strengthen trial design by addressing concerns regarding clinical variability. However, in rare diseases, many of which cause a shortened lifespan,[57] there are ethical concerns about placebo-controlled trials. Furthermore, parents may be reluctant to enroll their child in a trial where he or she may receive a placebo rather than the intervention under study. Balanced against the clinical researcher's desire to maintain equipoise is a likely assumption by hopeful families of an expected clinical benefit. In a rapidly progressing fatal disease, there is perhaps greater urgency on the part of parents to ensure their child is exposed to an active treatment condition, before the possible window of therapeutic opportunity is lost.

In the analysis of clinical trial data, rare diseases are at a dual disadvantage. By necessity, clinical trials in rare disorders enroll small samples. In combination with high inter-individual variability in clinical course observed in many rare diseases, this diminishes a study's power. Thus, alternative trial designs and statistical techniques that maximize data from a small and heterogeneous group of subjects are needed. Such approaches should maximize knowledge gain from each study, or introduce efficiency in sample size, including crossover, n-of-1, and adaptive design approaches.[58] There is precedent for approval of drugs with an orphan designation based on pivotal studies that are not randomized, placebo-controlled, or double-blind, with smaller trial sizes compared to studies of drugs without

such a designation.[59] When a compound fails, researchers must be clear that there is a true lack of biological effect, rather than failure due to inadequate study design.[60] Existing resources for investigators include the Office of Orphan Products Development Science of Small Clinical Trials annual course,[61] direct pre-Investigational New Drug application guidance from the Food and Drug Administration regarding trial design and outcomes, and the National Institute of Neurological Diseases and Stroke Network for Excellence in Neuroscience Clinical Trials (NeuroNEXT)[62] for early phase studies, where protocol working groups are formed to hone trial design for each study executed through the network, and network infrastructure facilitates multicenter participation and, thus, sample size optimization.

Natural History and Patient Registries

Detailed understanding of the natural history of disease is crucial to the design of clinical trials. By understanding the natural course of disease, key milestones in disease progression can be identified, an appropriate length of study to monitor change in disease progression can be selected, the most salient aspects of disease can be assessed, inclusion/exclusion criteria can be developed appropriately, and clinically meaningful difference can be determined. In rare disease, the small numbers of patients, geographic dispersion of patients, and small number of interested or adequately trained researchers have all been barriers to systematic collection of natural history data compared to common diseases. There is opportunity for clinical research collaboration to strengthen our knowledge of natural history and to establish prospective data appropriate for use as historical controls in the future. A clinical registry of prospectively obtained data may introduce efficiency into future studies by serving as a source for historical controls. Patient contact registries also have the potential to serve as powerful recruitment tools.[63,64]

Outcome Measures

Validated measures of disease activity or disease progression are often lacking in rare diseases. Existing clinical rating scales for the neuronal ceroid lipofuscinoses have improved our understanding of the natural history of disease,[22,65-67] but these scales may require further refinement for clinical trial use. Moreover, the clinical phenotype of the neuronal ceroid lipofuscinoses and many other rare diseases are heterogeneous, posing a challenge to selection of clinical endpoints that will be informative across the spectrum of disease expression. We must continue to refine our clinical rating scales to better quantify these multifaceted diseases, increase their precision related to small changes, and better address ceiling and floor effects. It is also crucial to engage families about meaningful outcomes. To complement clinical measures, there is a role for biomarker development to support proof-of-concept or to serve as surrogate outcomes. In addition, given the prominence of cognitive and behavioral symptoms in individuals with neuronal ceroid lipofuscinosis, knowledge of the cognitive and behavioral phenotype in animal models must be expanded in parallel so that the effects of potential treatments on these symptoms can be evaluated in the preclinical setting.[68] A working group meeting to refine and develop clinical trial outcome measures for juvenile neuronal ceroid lipofuscinosis will take place in late 2013.[69]

Subject Recruitment and Retention

Timely and adequate recruitment of eligible participants is a challenge for any rare disease. Often there is a desire to study patients with early disease for disease-modifying agents or, in contrast, those with advanced disease when the intervention risk is high. Yet where patients are few, it may not be feasible to significantly narrow entry criteria based on disease stage or other characteristics. Geographic dispersion of potential participants requires multicenter or even multinational collaboration on the part of investigators. In diseases with significant physical impairments, travel to research centers may pose an insurmountable

barrier to research participation. For trials involving repurposed drugs, recruitment and retention can also be threatened through off-label use outside of the clinical research setting. Technologies such as telemedicine can broaden access of investigators and patients to one another, and increase the reach of those with specific expertise.[70] Effective recruitment is also supported through partnership with patient organizations, patient contact registries, and clinician education to increase disease recognition and decrease time to diagnosis. Collaboration is needed between researchers and patient families to develop consensus regarding priorities as new therapies for clinical evaluation enter the pipeline, competing to recruit the same small population.

Drug Development and Funding

Unifying rare and common diseases is a desire on the part of stakeholders to shorten the drug development timeline. For central nervous system drugs, this takes on average 10 years, from submission of the Investigational New Drug application to the New Drug Application approval — the longest for any therapeutic class.[71] Preclinical development further lengthens this timeline. The success rate for approval of new central nervous system drugs is less than half of the approval rate for all other new drugs. The Food and Drug Administration Modernization Act of 1997[72] attempts to address these timeline concerns in rare diseases, with provisions for fast-track designation and accelerated approval paths without compromising safety and efficacy standards.

The process of new drug development is costly as well as time-consuming; pre-approval costs for a new compound may exceed $800 million.[73,74] Unfortunately, for rare, fatal, and rapidly progressing pediatric disorders, there is seldom access to large industry research and development dollars or the luxury of time. In comparison with common diseases, rare disease therapeutics are assumed to have small markets and thus small economic impact, providing little return on investment. The Orphan Drug Act developed incentives to stimulate interest in drug development for rare disease, including protocol assistance from the Food and Drug Administration, tax credits, fee-waivers for regulatory submissions, and 7 years of market exclusivity. There is increasing recognition that therapeutics for orphan diseases are indeed profitable avenues of development.[75,76] The Orphan Drug Act has successfully raised industry attention to rare diseases. Since its initiation, 390 drugs and biologics have been approved under orphan drug status, compared with 10 drugs approved for rare disease indications in the 1970s, just before enactment.[75]

In the current economic climate, funding has become increasingly competitive, with a desire on the part of funding agencies to have broad public health impact for each dollar spent. For academic scientists, there is opportunity to make use of existing preclinical drug discovery resources such as the NIH National Center for Advancing Translational Sciences, also known as NCATS. Within this center, the Therapeutics for Rare and Neglected Diseases, or TRND, program aims to stimulate drug discovery and speed development of new and repurposed drugs not through funding dollars, but through access to Investigational New Drug-enabling preclinical research resources. This is an opportunity for academic scientists to accelerate development of new interventions for neuronal ceroid lipofuscinosis.

Researcher Training

Lastly, there is a paucity of clinical researchers with interest, training, and experience in the design and execution of trials for rare disorders. Clinical researchers in academia face challenges of balancing clinical demands and research, navigating regulatory hurdles, lack of local infrastructure, and need for training in clinical research. We have an opportunity to engage students and trainees in research and to expand and strengthen training programs in experimental therapeutics.[77] The National Institutes of Health career-training grant

opportunities provide support, mentorship, and protected time for bench and clinical researchers to develop expertise in many areas relevant to rare disease research. In recent years, the National Institute of Neurological Diseases and Stroke Clinical Trials Methods Course has provided a venue for intensive training in clinical trial design and execution for neurological disorders.[78]

Conclusion

Experimental therapeutics for rare disorders faces many challenges. Despite these challenges, there have been several recent accomplishments in the neuronal ceroid lipofuscinoses, including initial development of disease-specific rating scales, funding to further develop outcome measures for juvenile neuronal ceroid lipofuscinosis, and several ongoing clinical trials. Future priorities are to continue to improve our understanding of animal model phenotypes, disease pathophysiology, and natural history, to improve our existing quantitative measures and to hone a patient-centered approach. Continued efforts to build clinical trial design expertise and infrastructure and efforts toward research prioritization will support the future directions of therapeutic development in the neuronal ceroid lipofuscinoses.

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Table 1

Published Reports – Neuronal Ceroid Lipofuscinosis Therapeutics

NCL Type	Intervention	Indication	Sample Size	Outcome Measure	Follow-up Duration	Conclusion	Ref.
Secondary analysis							
JNCL	Flupirtine	Disease modification	45	UBDRS	1-8 years	Ineffective	8
Case series							
JNCL	Antioxidants (vitamin E, vitamin C, methionine, BHT, sodium selenite)	Disease modification	74	(1) IQ, (2) JNCL CRS, (3) plasma selenium levels, glutathione peroxidase activity, serum vitamin B2, B6, and E levels, (4) clinical signs and symptoms	6-18 years	Possibly effective, overall inconclusive	18
LINCL	Bone marrow transplantation	Disease modification	2	(1) Cellular inclusions by EM, (2) clinical signs and symptoms	2 years	Inconclusive	9
INCL	Lamotrigine	Epilepsy	16	Clinical signs and symptoms	3 weeks - 5.8 years	Effective	79
LINCL, JNCL	Bone marrow transplantation	Disease modification	2	Clinical signs and symptoms	1-3 years	Inconclusive	10
JNCL	Lamotrigine	Epilepsy	28	(1) IQ, (2) Clinical signs and symptoms	1 year	Effective	80
JNCL	Antiepileptics	Epilepsy	60	Clinical signs and symptoms	1 year	Effective	81
INCL	Hematopoietic stem cell transplant - umbilical cord blood (n = 2), bone marrow transplant (n = 1)	Disease modification	3	(1) PPT1 enzyme activity (leukocytes and CSF), (2) storage material, (3) clinical signs and symptoms	2-4 years	Possibly effective	11
LINCL	Bone marrow transplantation	Disease modification	1	(1) TPP1 enzyme activity, (2) clinical signs and symptoms	3 years	Ineffective	12
JNCL	Pallidotomy and deep brain stimulation	Dystonic storm	2	(1) Fahn-Marsden dystonia rating scale, (2) clinical signs and symptoms	7 months - 6 years	Effective	82
Open-label, single-group clinical trials							
JNCL	Polyunsaturated fatty acids	Disease modification	5	(1) Serum lipoproteins, (2) IQ, (3) clinical signs and symptoms	1 year	Inconclusive	15
LINCL, JNCL	Antioxidants (selenium, Vitamin E)	Disease modification	3	(1) Selenium, vitamin E, glutathione peroxidase levels, (2) clinical signs and symptoms	6 months - 1.75 years	Inconclusive	83
JNCL	Polyunsaturated fatty acids	Disease modification	6	(1) IQ, (2) test of motor impairment, (3) British ability scales, (4) clinical signs and symptoms	4 -7 years	Possibly effective	16

NCL Type	Intervention	Indication	Sample Size	Outcome Measure	Follow-up Duration	Conclusion	Ref.
JNCL	Psychotropic medications (citalopram, olanzapine, risperidone, quetiapine)	Psychotic and affective symptoms	14	Clinical signs and symptoms	3 months - 5 years	Effective	84
INCL	Transdermal fentanyl	Pain	5	Visual analogue pain scale	15 days	Partially effective	85
JNCL	Prednisolone	Disease modification	8	(1) UPDRS, (2) serum GAD antibodies, (3)clinical signs and symptoms	1 year	Possibly effective	14
Open-label, historical-control clinical trial							
JNCL	Antioxidants (vitamin E, vitamin B2, vitamin B6, selenium)	Disease modification	43	(1) JNCL CRS, (2) clinical signs and symptoms	8 years	Possibly effective	20
Open-label, parallel-group clinical trials							
JNCL	Antioxidants	Disease modification	46	1) IQ, 2) Clinical signs and symptoms		Possibly effective	19
JNCL	Antioxidants	Disease modification	125	(1) IQ, (2) plasma selenium levels, glutathione peroxidase activity, serum vitamin E level, (3) clinical signs and symptoms	4-11 years	Partially effective	17
JNCL	Levodopa or selegiline	Parkinsonism	21	UPDRS	12 months	Effective (levodopa)	86
Single-blind, placebo-controlled clinical trial							
INCL, LINCL, JNCL	Melatonin	Sleep disturbance	5	(1)Actigraphic recordings, (2)sleep log, (3) parent-reported sleep quality	3 weeks per treatment arm (3 arms per subject)	Ineffective	87
Randomized, placebo-controlled, clinical trial							
JNCL	Antiparkinsonian drugs (orfenadrine, amantadine, levodopa + benserazide)	Parkinsonism	8	(1) Motor CRS, (2) ratings of videotaped tasks	11-13 weeks per treatment arm (3 arms per subject)	Ineffective	88

BHT, butylated hydroxytoluene; CRS, clinical rating scale; EM, electron microscopy; GAD, glutamic acid decarboxylase; INCL, infantile neuronal ceroid lipofuscinosis; IQ, intelligence quotient; JNCL, juvenile neuronal ceroid lipofuscinosis; LINCL, late-infantile neuronal ceroid lipofuscinosis; PPTl, palmitoyl protein thioesterase 1; Ref, reference; TPP1, tripeptidyl peptidase 1; UBDRS, Unified Batten Disease Rating Scale; UPDRS, Unified Parkinson Disease Rating Scale.

Table 2

Neuronal Ceroid Lipofuscinosis Clinical Trials Registered on www.clinicaltrials.gov

NCL Type	Intervention	Sample Size	Trial Phase	Design	Current Status	Clinicaltrials.gov Identifier
LINCL	Gene transfer vector (AAV2CUhCLN2)	11	I	Single-group, Open-label	Ongoing, not recruiting	NCT00151216[25]
LINCL	Gene transfer vector (AAVrh.l0CUCLN2)	16	I	Parallel-group, Open-label	Ongoing, recruiting	NCT01161576[24]
LINCL	Gene transfer vector (AAVrh.l0CUCLN2)	8	I/II	Parallel-group, Open-label	Ongoing, recruiting	NCT01414985 [28]
JNCL	Mycophenolate mofetil (CellCept)	30	II	Randomized, placebo-controlled, crossover	Ongoing, recruiting	NCT01399047[27]
INCL, LINCL	Cysteamine (Cystagon) + N-acetylcysteine (Mucomyst)	10	II	Single-group, Open-label	Ongoing, not recruiting	NCT00028262 [26]
INCL, LINCL	Human CNS stem cell transplantation	0	Ib	Single-group, Open-label	Terminated	NCT01238315[23]
INCL, LINCL	Human CNS stem cell transplantation	6	I	Single-group, Open-label	Completed	NCT00337636 [13]

AAV, adeno-associated virus; CNS, central nervous system; INCL, infantile neuronal ceroid lipofuscinosis; JNCL, juvenile neuronal ceroid lipofuscinosis; LINCL, late-infantile neuronal ceroid lipofuscinosis; NCL, neuronal ceroid lipofuscinosis.