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Current Therapeutic Approaches in Leukodystrophies: A Review

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Abstract

Leukodystrophies are a heterogeneous class of genetic diseases affecting the white matter in the central nervous system with a broad range of clinical manifestations and a frequently progressive course. An interest in precision medicine has emerged over the last several decades, and biomedical research in leukodystrophies has made exciting advances along this front through therapeutic target discovery and novel disease model systems. In this review, we discuss current and emerging therapeutic approaches in leukodystrophies, including gene therapy, antisense oligonucleotide therapy, CRISPR/CAS-based gene editing, and cell and stem cell based therapies.

Keywords

leukodystrophy; clinical trial; therapeutic targets; neurogenetics

Leukodystrophies are a heterogeneous class of genetic diseases affecting the white matter in the central nervous system with a broad range of clinical manifestations and a frequently progressive course. Although each of these diseases is individually quite rare, collectively, leukodystrophies may affect as many as 1 in 7500 people.^{1,2} In the 20th century, advances in genetic medicine led to the identification of specific genetic and biochemical defects associated with individual leukodystrophies such as adrenoleukodystrophy, metachromatic leukodystrophy (MLD), Krabbe disease, Alexander disease, and Canavan disease. With these scientific advances has come the hope for curative therapies to correct these defects.

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The last several decades have introduced an effort toward precision medicine—with targeted therapeutic strategies for an individualized approach to health care, incorporating both genetic and environmental variables into a patient-specific care plan. Biomedical research in leukodystrophies has made exciting advances along this front through therapeutic target discovery and novel disease model systems. Clinical research has also made important progress with natural history studies and emerging clinical trials. However, the biggest challenge to finding a cure for this family of diseases has been designing effective outcome measures, biomarkers, and clinical proof of concept models that bridge the ravine between natural history and therapeutic trials.

In this article, we review current and emerging therapeutic approaches in leukodystrophies, including gene therapy, antisense oligonucleotide therapy, CRISPR/Cas-based gene editing, and cell and stem cell based therapies (Table 1). While we will discuss these approaches as potential treatment options for leukodystrophies, we will also use clinical evidence from genetic diseases other than white matter disorders as examples of current successes or future directions.

How to Fix Genetic Disease

There are several targets along the pathophysiologic cascade to consider in an approach to cure genetic disease (Figure 1). These targets include correcting specific gene or protein defects to prevent disease onset, arresting disease progression, restoring function to structures that have been damaged, and overcoming pathophysiology with alternative or compensatory mechanisms. When a genetic disease results in no product or insufficient active gene product, a gene delivery approach is ideal, commonly referred to as gene therapy. In contrast, when a genetic disease results in altered function or too much of a gene product, a gene silencing or gene editing approach is employed.

Gene Therapy

Over the last several decades, gene therapy has been increasingly used in clinical trials for a variety of indications affecting all organ systems, with more than 2500 total gene therapy trials worldwide since the 1990s; nearly 2% of these address neurologic disease.³

Gene therapy employs several techniques that may be categorized based on the method of gene delivery. In vivo gene therapy typically uses a viral vector that is administered either systemically via an intravenous catheter or intraparenchymally by injection directly into the target organ or tissue (eg, brain, liver).⁴ In ex vivo gene therapy, a patient's cells are collected and hematopoietic stem cells or other blood-derived cells are isolated from the blood. These patient-derived cells are then mixed with a replication-incompetent retrovirus that has been modified to include a therapeutic gene. As the virus integrates into the hematopoietic stem cell genome, a healthy genotype is restored to the cell and these transduced cells are reintroduced to the patient.⁴

Lentiviruses are the most commonly used ex vivo gene therapy vectors. These are retroviruses that are genetically modified to become replication incompetent. They include a single-stranded ribonucleic acid (RNA) genome with a reverse transcriptase enzyme that

encodes deoxyribonucleic acid (DNA) that integrates randomly into the human genome.⁴ Clinical trials using lentiviral gene transfer into hematopoietic stem cells are currently ongoing in adrenoleukodystrophy, and MLD and preliminary results show both safety and therapeutic benefit.^{5,6} Preclinical trials in mice for Krabbe disease also show promise.⁷

The biggest advantage of this technique is that insertion of the therapeutic gene into human DNA allows for lasting expression of the gene. However, many concerns also exist for this technique. Because the lentivirus inserts randomly into the human genome, there is risk of clonal expansion of the gene if inserted into a vulnerable site, which can lead to oncogenesis. This random insertion may also result in overexpression of the target gene in tissues or organs where it may not ordinarily be expressed in normal physiology. Detrimental effects may occur if, for instance, a protein typically expressed in the liver is expressed in the brain or vice versa. Additional concerns arise with respect to the viral vector itself. While inactivated, the lentivirus may have the capability to become replication competent, particularly with broader targets of the capsid. The viral vector may also trigger a severe immune response.

Adeno-associated viral (AAV) vectors are an alternative method of gene therapy that utilize adenovirus, a nonenveloped double-stranded DNA virus, as a vector for gene delivery and are often used for in vivo gene therapy. AAV vectors have several serotypes that can target specific cells to correct disease-causing improper protein function in that cell population. Prior to administration, AAV genetic material is replaced with a therapeutic gene that, once in the human cell, is translated to restore the natural function of disrupted proteins. At least 11 AAV serotypes have so far been identified, each with tropism for specific cells within organ systems. This makes it possible to target specific tissues to which the gene will be delivered. Within the central nervous system (CNS), AAV1, AAV2, AAV4, AAV5, AAV6, AAV8, and AAV9 have all been used. Most recently, a new capsid serotype, AAV Olig001, has been developed as a chimera of several other serotypes that specifically targets CNS oligodendrocytes and spares other systemic organs such as the liver.⁸

In contrast to lentivirus, once inside the cell the AAV genome does not randomly integrate into the nuclear DNA but can be engineered to insert in so-called Safe Harbor Sites, thus reducing the likelihood of oncogenesis.⁹ AAV also have similar challenges to lentiviral gene therapy in that systemic injection may result in expression of the gene in the wrong tissue. Alternatively, immune response against the virus—depending on the choice of serotype—may result in antibodies against both the virus and the gene product, resulting in inactivation of subsequent administration of therapy or systemic inflammatory response.

A recent clinical trial in Canavan disease attempted to address some of these challenges. The trial used AAV2 containing the *ASPA* gene injected surgically directly into the brain.¹⁰ Thirteen patients with Canavan disease received the intervention versus 15 untreated controls. Five-year outcomes of this trial showed reduction in seizures and less atrophy in cases that received early treatment.¹¹ Although this technique is promising, it is limited in that it is a major surgical intervention that did not show dramatic improvements in neurologic or functional outcomes in Canavan disease.

Another recent study of spinal muscular atrophy type 1 (SMA1) holds the greatest promise yet for gene therapy in childhood-onset neurogenetic disorders. SMA1 is a devastating degenerative neuromuscular disease that causes motor failure and death during infancy. In this study, 15 infants with SMA1 were administered AAV9 with DNA encoding the *SMN1* protein, which is absent in this disease, via intravenous infusion. The safety profile of this therapy was favorable and, at only the 3-month follow-up, the cohort treated at a high dose was found to improve in measures of motor development when compared with historical cohorts without therapy who had declined. Strikingly, all patients survived at 20 months of age compared with only 8% of patients in historical SMA1 natural history cohorts.¹² At 2 years, no waning effect or clinical regression was observed, but long-term outcomes in these patients are still being investigated.¹²

Another AAV gene therapy trial is under way for giant axonal neuropathy, a disease of neurofilaments that initially presents with peripheral nervous system manifestations but frequently progresses to CNS involvement (<http://Clinicaltrials.gov> NCT02362438). This phase I trial uses scAAV9 administered intrathecally and the study is still ongoing.

A promising preclinical trial in Pelizaeus-Merzbacher-like disease, a leukodystrophy resulting from mutations in gap junction gene connexin 47, used an AAV to restore this gene via intracerebral injection in mice. Treated mice showed improved survival and motor outcomes over controls as well as pathological improvements in myelination, reduced cell death and reduced astrogliosis.¹³ In Krabbe disease, a mouse model injecting an AAV intravenously and into the brain resulted in longevity, good nutrition, and similar behavior to control mice.¹⁴

Antisense Oligonucleotide Therapy

Antisense oligonucleotide therapy is a gene-silencing technique that uses antisense RNA to prevent the translation of mRNA into disease-causing proteins by binding to them. Antisense DNA may also be used to target a specific complementary RNA. In some cases, antisense oligonucleotides are used to turn off mutated genes with associated gain of function (eg, glial fibrillary acidic protein in Alexander disease). In others, they are used to block premature gene splicing and hence result in an intact or functional gene product when there previously was none (eg, dystrophin in Duchenne muscular dystrophy).¹⁵ The advantage to this technique is that it is highly specific in its site of hybridization, can be manufactured in large quantities, and does not require a viral vector. Limitations include a short half-life in plasma, difficulty in directing the therapy to specific cells (particularly across the blood-brain barrier), a large dose requirement for therapeutic response and vulnerability to nucleolysis.

Recently, the antisense oligonucleotide therapy, nusinersen, received approval by the US Food and Drug Administration for treatment of SMA1. Nusinersen is an antisense oligonucleotide that is designed to alter pre-messenger RNA and modify splicing of the *SMN2* gene, increasing production of the *SMN2* protein that compensates for missing *SMN1* in this disease. This drug is administered intrathecally in several doses to achieve a loading dose at 3 months and then every 4 months thereafter. The initial clinical trial of

nusinersen was terminated early after half of the infants showed progress in motor milestones versus none of the control group. Final analyses revealed that nusinersen improved survival and reduced the rate of need for permanent ventilatory support.^{16,17} With its recent approval, this antisense oligonucleotide therapy has the potential to dramatically impact the lives of patients and families affected by this devastating disease.

This technique has shown promise in the animal model of Alexander disease, but has not yet been studied in human leukodystrophies.¹⁸

CRISPR/Cas System–Based Gene Editing

Clustered Regularly Interspaced Short Palindromic Repeat (CRISPR) is a relatively new gene-editing technique that has revolutionized genetic research over the last few years and holds promise as a future therapy for leukodystrophies. CRISPR takes advantage of a series of repetitive sequences in DNA that are used as part of the immune system of bacteria to recognize viral DNA. Together with a Cas9 endonuclease enzyme, the CRISPR/Cas9 complex has the capacity to scan a cell's genome and cut it at a desired location. It can then be guided to replace the target gene with a new one. This offers several advantages over the gene therapy techniques discussed above because it not only targets a site specifically on the genome and allows cutting out the mutated sequence, but also allows to replace it with the correct sequence.¹⁹

CRISPR technology has been used to quickly create new animal models for human disease that previously may have taken years to develop. Therapeutically, delivery of CRISPR alone has been shown to normalize disease phenotypes in mouse models of Duchenne muscular dystrophy and other genetic diseases.^{20,21} Other studies have successfully corrected genetic mutations in human induced pluripotent stem cells ex vivo.^{22,23} Several proof-of-concept animal models have emerged that use a variety of delivery systems to administer CRISPR including AAV and lipid nanoparticles. However, before CRISPR mediated gene editing is ready for clinical trials in humans, more research on optimal delivery methods is needed.¹⁹ It is likely that the first applications will be in diseases where dominant mutations resulting in gain of function are cut out, such as mutations in *GFAP*, *SCN1A*, *FMRP*, etc.

Cell and Stem Cell Based Therapies

Cell and stem cell based therapies for leukodystrophies attempt to halt or reverse disease progression by allowing donor stem cells to repopulate and deliver restored enzymes to various tissues.^{24–26} Hematopoietic stem cell transplantation is a well-established intervention that has been widely used not only for oncologic indications such as leukemia and lymphoma but has also been explored as a therapy for genetic and autoimmune diseases, including several leukodystrophies.^{27–31} Hematopoietic stem cells are most frequently derived from the bone marrow (commonly referred to as bone marrow transplant) but may also be derived from the peripheral blood or umbilical cord blood. Although this therapy is available at academic hospitals throughout the United States and its safety has improved over time, it does not come without risk.³² In leukodystrophies, allogeneic hematopoietic stem cell transplantation is associated with a high risk of mortality, ranging from 8% to 22%

depending on the patient's age, baseline disease, and other factors.^{33,34} There is also high morbidity as a result of graft versus host disease and potent chemotherapy regimens that may result in serious infection, end-organ damage, or long-term chronic health conditions.^{32,35} Despite this high-risk profile, bone marrow transplant has been found to be beneficial in approximately 20 neurometabolic disorders.³⁶ Although this therapy may prove some benefit to change the natural history of disease in these complex patient populations, hematopoietic stem cell transplantation may not always lead to a cure.

Allogeneic hematopoietic stem cell transplantation entails harvesting donor peripheral blood stem cells via leukapheresis after stimulation with granulocyte colony-stimulating factor. These cells are then transplanted into the patient recipient after immunosuppression with chemotherapy and radiation to prevent graft rejection. Until donor engraftment occurs, patients are at high risk of systemic infection due to immunosuppression, which is associated with major morbidity and mortality. The intensive chemotherapy protocols that are required for adequate immunosuppression also pose detrimental risks due to chemotoxicity.

Hematopoietic stem cell transplantation is recognized as the only treatment to improve survival in boys with cerebral adreno-leukodystrophy when performed in early stages of the disease. This therapy improved survival from 54% to 95% at 5 years and from 42% to 95% at 10 years.³⁷⁻³⁹ In patients with magnetic resonance imaging (MRI) severity scores of less than 10 at the time of transplant, disease progression has been found to stabilize on neuroimaging measures as well as on clinical measures of motor and cognitive function.⁴⁰ However, despite stabilization and good survival, many patients are left with long-term neurocognitive impairments at a rate of up to 67%, particularly those with higher MRI severity scores at the time of transplant.⁴¹ Given the importance of early intervention to improve outcomes, adrenoleukodystrophy has been added to the list of diagnoses included on the newborn screen in several states, including New York, Connecticut, Minnesota, Pennsylvania, and California.⁴²

Transplantation of umbilical cord blood has been used in Krabbe disease. Initial results in 2005 were very promising, with 100% engraftment and 100% survival at 3 years among 11 asymptomatic newborns. In contrast, 14 symptomatic infants had only 43% survival at 3 years. Although it was initially reported that the asymptomatic newborns made excellent developmental progress with only mild delays at 3 years, long-term follow-up of these patients was published in 2009, reporting that as these children age, they develop progressive neurologic deterioration with spasticity, motor and language regression, acquired microcephaly, and failure to thrive.⁴³ The cause and extent of this long-term deterioration is still under investigation, and although children with Krabbe disease who have undergone umbilical cord blood transplants functionally improve over the fulminant natural history of this disease, they still incur a significant neurologic disability burden.

Finally, neural stem cells have also been used in clinical trials of leukodystrophies. A phase 1 study in early severe Pelizaeus Merzbacher disease surgically implanted fetal brain-derived neural stem cells into 4 sites within the deep white matter of 4 patients using MRI guidance.⁴⁴ Although the study was successful in demonstrating safety of this procedure and

subsequent immunosuppressive protocol, as well as some improvement in MRI metrics within the white matter,⁴⁴ the company sponsoring the study went bankrupt.

Neural stem cell implantation may still be a promising venue for future clinical trials, but several challenges exist. Obtaining fetal brain-derived stem cells is not only limited and costly, but may be politically controversial. In addition to the risks associated with the immunosuppression required for engraftment, there is also concern for malignant conversion of these cells and graft versus host disease. Autologous induced pluripotent stem cells (iPSC) could undergo ex vivo gene correction prior to transplantation, as is currently done with hematopoietic stem cells.

Challenges and Ethical Concerns

Despite remarkable advances in therapeutics for leukodystrophies over the last decade and many promising scientific advances, several practical and ethical challenges exist that must be overcome for these treatments to move from the laboratory bench to clinical trials and finally through regulatory approval by federal agencies.

Before many clinical trials can move forward, better quantitative outcome measures and comparative natural history data must be established in order to test the effectiveness of novel therapeutics. Although some leukodystrophies have validated biomarkers, others have none. However, this effort has been impeded by the fact that leukodystrophies are a clinically heterogeneous group of diseases.² An appropriate outcome measure for one type of leukodystrophy may not be appropriate for another, and disease-specific outcome measures are needed for each clinical trial. Clinical phenotypes or rate of progression may also differ within a single disease, making it difficult to compare patient groups. For example, Alexander disease may have onset at different ages (infantile, juvenile, or adult) with different neurologic manifestations and adrenoleukodystrophy may present as cerebral adrenoleukodystrophy or adrenomyeloneuropathy (AMN). A variable or slowly progressive disease course can also be difficult to quantify over time and lead to a need for clinical trials with larger patient cohorts over a longer period of time, compounding the already high costs of clinical trials.

Further, measures that are quantitative and sensitive for disease progression or severity alone are not sufficient. “Clinically meaningful” outcomes are now required as part of clinical trial design and regulatory approval by the United States Food and Drug Administration (FDA) and, similarly, patient-centered outcome measures are increasingly emphasized in clinical research.^{45,46} These measures (such as quality of life) not only need to be quantifiable, but they should correlate with other scientific biomarkers such as advanced neuroimaging, serum metabolic biomarkers, or motion analysis techniques.^{47–49} Finally, yet another challenge arises when a therapy does not achieve a “cure” for a given disease but may still have some clinical benefit. In this scenario, how can subtle clinical differences be measured? Given the rarity of these diseases, consortia are needed to pool patients and data and develop quantitative disease-specific databases with outcome measures.

Recruitment for clinical trials is also a challenge, and several barriers exist. First, leukodystrophies are rare and overall prevalence is low, leading to few eligible patients. Also, delay in diagnosis is common leading to increased burden of irreversible disease at the time of diagnosis. For these reasons, newborn screening has been advocated for Krabbe disease and has been implemented for adrenoleukodystrophy in several states in the United States.^{50–52}

The immense costs of both the therapeutic technologies themselves and the clinical trials for this group of diseases is not only a pragmatic challenge to justify funding by drug companies or grants, but also presents several ethical concerns. If clinical trials are successful, the cost of the drug and/or hospitalization for procedure may be immense and duration of treatment, particularly for gene therapies, may be unclear. This ethical challenge has most recently been discussed regarding nusinersen for SMA.⁵³ High health care costs also exacerbate health care disparities both within and between developed versus developing countries. Access to novel therapeutics or even clinical trials may only be available to those patients with the financial means to obtain them in academic clinical centers.^{54,55}

Supportive Care

Although research to develop useful biomarkers and to implement clinical trials is ongoing, symptomatic management is critical in the care of patients who currently have leukodystrophies.⁵⁶ A multidisciplinary approach is needed that includes multiple medical specialties and allied health professionals as the majority of children and adults with leukodystrophies may be affected by cognitive, motor, endocrine, pulmonary, and gastrointestinal symptoms. Psychosocial challenges are also common for families affected by neurodegenerative diseases, and genetic counseling is needed for family members who may be carriers. Although detailed guidelines regarding management of these issues is beyond the scope of this review, the Global Leukodystrophy Initiative Consortium has provided a consensus statement on the preventive and symptomatic care of patients with leukodystrophies.⁵⁶

Future Directions and the Need for Consortia

All of the above emerging therapies for leukodystrophies have changed the tone of conversation about these neurodegenerative diseases from bleak to hopeful over the last decade. As genetic medicine continues to progress with new therapeutic technologies and techniques rapidly evolving, effective biomarkers and clinical outcomes measures must also be developed in parallel for clinical trials to be successful. To facilitate this, collaborative consortia that connect research teams both nationally and internationally are of paramount importance. These consortia, such as ALD Connect and Hunter's Hope for Krabbe disease, unite patients, families, physicians, and researchers to establish standardized data collection across sites, create standard protocols for clinical trials, and incorporate patient-centered outcome measures. This collaborative approach holds promise to advance therapeutic opportunities for these rare diseases in the decades to come.

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Figure 1.

Approaches to curing leukodystrophies: consideration of different targets along the pathophysiological cascade from gene defect to gene product to disease progression and damaged white matter. One may target the specific gene defect or protein defect, arrest disease progression, or restore function to structures that have been damaged. Each of the approaches discussed in this article are illustrated at the point at which they target disease. AAV, adeno-associated viral vectors; ASO, antisense oligonucleotide therapy; CRISPR, clustered regularly interspaced short palindromic repeat; LVGT, lentiviral vector gene therapy.

Table 1.

Therapeutic Approaches for Leukodystrophies and Current Evidence.

Approach	Advantages	Drawback	Clinical trials (disease, author)	Description
Lentiviral Gene Therapy (ssRNA + RT; ex vivo)	<ul style="list-style-type: none"> • Expression of normal gene copy for diseases with loss of function mutations • Random insertion of gene allows for lasting expression. 	<ul style="list-style-type: none"> • Random insertion into genome → Risk of clonal expansion/oncogenesis • Risk of overexpression in nontarget tissues/organs • Risk of virus becoming activated • Risk of severe immune response 	ALD (Eichler et al ³³); MLD (Sessa et al ⁵ ; Biffi et al ⁶)	Ex vivo transduction of hematopoietic stem cells and replacement following myeloablation; preliminary results in ALD and MLD show safety and arrest of disease progression.
Adeno-associated viral vector gene therapy (dsDNA; in vivo)	<ul style="list-style-type: none"> • Expression of normal gene copy for diseases with loss of function mutations • Specific serotypes have tropism for specific organs/cell types • May integrate into "Safe Harbor Sites" → reduced risk of oncogenesis 	<ul style="list-style-type: none"> • Risk of overexpression in non-target tissues/organs • Risk of virus becoming activated • Risk of severe immune response • Risk of immune response inactivating subsequent administration 	Canavan disease (Janson et al ¹⁰ ; Leone et al ¹¹)	Surgical injection with AAV2 into brain tissue; reduction seizures, less atrophy.
Antisense oligonucleotide therapy	<ul style="list-style-type: none"> • Silences genes in diseases with excess or detrimental gene product • May also block premature splicing of genes in diseases with nonfunctional genes • Highly specific site of hybridization • No viral material 	<ul style="list-style-type: none"> • Short half-life in plasma → difficult to direct to specific cells or across blood-brain barrier • Large dose requirement • Vulnerability to nucleolysis 	None currently	
CRISPR/Cas gene editing	<ul style="list-style-type: none"> • Targets specific site in genome • Able to cut, edit, or replace sequence. 	<ul style="list-style-type: none"> • Early stages of research, undergoing proof-of-concept animal models • Unknown optimal delivery methods 	None currently	
Hematopoietic stem cell transplant	<ul style="list-style-type: none"> • May be derived from bone marrow, peripheral blood, or umbilical cord blood • Available in most academic medical centers 	<ul style="list-style-type: none"> • High risk of mortality • Risk of graft versus host disease • Risk of infections secondary to immunosuppression • Risk of end-organ damage/long-term side effects of chemotherapy 	ALD (Moser et al ³⁷ ; Peters et al ³⁸ ; Mahmood et al ³⁹) Krabbe disease (Duffner et al ⁴³)	Arrested ALD progression when performed in early stages of disease. Short-term benefits in Krabbe but neurologic deterioration long-term.
Neural stem cell implantation	<ul style="list-style-type: none"> • Induced pluripotent stem cells may be useful 	<ul style="list-style-type: none"> • Fetal brain-derived stem cells is costly, controversial • Invasive implantation • Immunosuppression required for engraftment • Potential for oncogenesis • Potential for graft versus host disease 	Pelizaeus-Merzbacher disease (Gupta et al ⁴⁴)	Safety demonstrated, improvement in MRI metrics.

Abbreviations: ALD, adrenoleukodystrophy; MLD, metachromatic leukodystrophy; MRI, magnetic resonance imaging;