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Alexander Disease: Scientific Advancement and Therapeutic Intervention in Rare Disease Research

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ABSTRACT

Alexander Disease (AxD) is a rare, heritable white matter condition, or leukodystrophy, that helps to understand how collaborative, translational research can identify therapeutic options in a complex illness. AxD is a rare disease, first described in 1949, that affects approximately one in 2.7 million births. The disease hinders the function of the central nervous system (CNS) through the biotoxic overproduction of protein aggregates which cause the deterioration of the myelin sheath. Given the extreme rarity of AxD, disease-specific research is relatively limited, and there is no disease-modifying treatment currently available. At present, a clinical trial is underway to examine the safety and efficacy of Ionis Pharmaceuticals' ION373, an Antisense Oligonucleotide (ASO), that has reported success in preventing the progression of AxD in mouse models. This paper reviews the key components of AxD, therapeutic designs for AxD, and ultimately suggests future directions to optimize the therapeutic approach. This review also aims to promote rare disease awareness, as scientific progress for conditions like Alexander Disease is achieved through advocacy and promotion.

Introduction

Alexander Disease (AxD) is a rare leukodystrophy, affecting approximately one in 2.7 million births (Yoshida *et al.*, 2011). AxD is caused by a mutation in the *GFAP* gene that promotes the overproduction of glial fibrillary acidic protein (GFAP) in the central nervous system (CNS) (Messing *et al.,* 2012). As a result, the myelin sheath undergoes degradation, and a person affected by Alexander Disease experiences a progressive regression of various developmental milestones (Messing *et al.,* 2012). Myelin appears in the white matter, insulating neurons in the brain and the spinal cord to optimize the speed and transmission of signal conduction (Susuki, 2010). If myelin does not form correctly or degrades over time, there can be significant negative consequences, as seen in AxD.

AxD generally presents in four distinctive forms– neonatal, infantile, juvenile, and adult (Srivasta *et al.,* 1993). While similar, these different forms vary based on age of symptom onset and in their symptom severity. Across this clinical spectrum, there is a well-cited relationship between the age of diagnosis and the severity of symptoms (Srivasta *et al.,* 1993). Cases with earlier ages of diagnosis are correlated with more severe symptoms (Srivasta *et al.,* 1993). Therefore, the neonatal and infantile forms of Alexander Disease correspond with more severe clinical presentations, while the juvenile and adult forms display similar, but less severe, symptoms (Prust *et al.,* 2011).

Key Components of Alexander Disease

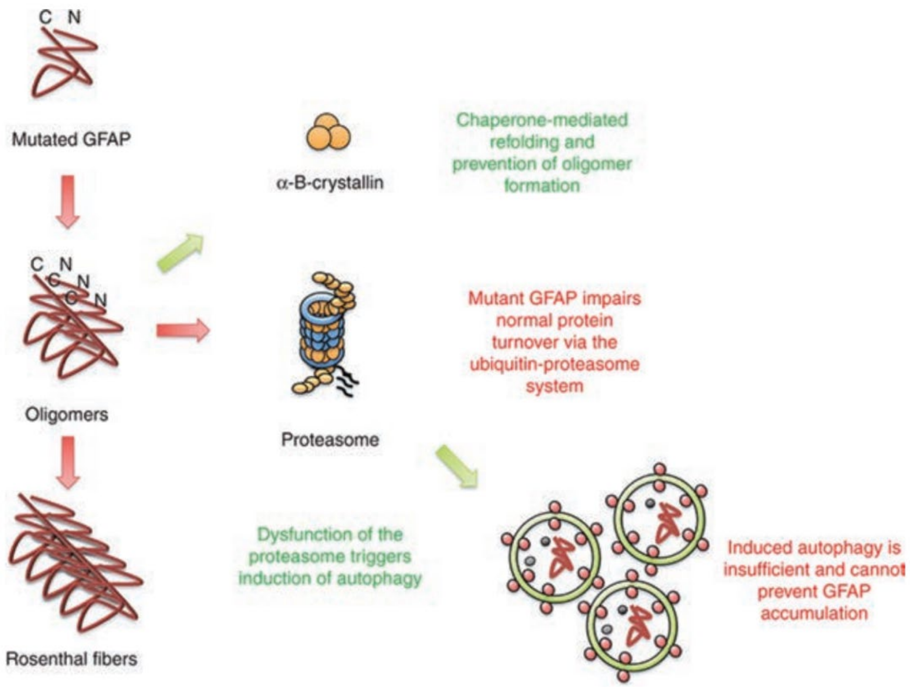

Figure 1. Overview of the Alexander Disease mechanism.
(Pascual, 2017)

GFAP Gene

The mechanism of Alexander Disease is complex, and several downstream biochemical pathways are implicated in this condition *(Figure 1)*. Generally, AxD is caused by a monogenic, pathogenic mutation in *GFAP,* a gene that encodes the GFAP protein (Messing *et al.*, 2012).

Almost all pathogenic mutations in the *GFAP* encoding gene are heterozygous single base pair changes in an affected individual's deoxyribonucleic acid (DNA) sequence (Hagemann *et al.*, 2006). The two most frequent mutation sites have been observed at Arg79 (most predominantly Arg79Cys and Arg79His) and Arg239 (most predominantly Arg239Cys and Arg239His) (Hagemann *et al.*, 2006). Approximately half of all published patients experience a mutation at either of these two sites (Hagemann *et al.*, 2006).

GFAP Protein

GFAP mutations are autosomal dominant and have dangerous gain-of-function effects (Quinlan *et al.*, 2007). For example, a pathogenic *GFAP* mutation can cause an overaccumulation of GFAP protein, which is a far-spanning protein that is found throughout the CNS (Hol and Pekny, 2015). GFAP is generally classified as an intermediate filament protein, which provides support and stability to cells, but the protein has a variety of other functions (Middeldorp and Hol, 2011). In AxD, GFAP accumulation almost always directly correlates to the severity of symptoms (Jany *et al.*, 2013). Thus, individuals with AxD who have higher GFAP protein expression exhibit worse symptoms compared to patients with less GFAP protein expression (Jany *et al.*, 2013).

The GFAP protein is composed of 432 amino acids (Messing and Brenner, 2020). Currently, mutations in 36 of these amino acids have been shown to cause AxD (Quinlan *et al.*, 2007). The majority of AxD-causing mutations are *de novo* amino acid substitutions (Quinlan *et al.*, 2007). *De novo* mutations occur spontaneously in the genome. According to the National Cancer Institute, "A *de novo* mutation can occur in an egg or sperm cell of a parent, in the fertilized egg soon after the egg and sperm unite, or in another type of cell during embryo development." Current studies show that more than 90% of AxD patients experience *de novo* mutations that manifest as AxD (Zang *et al.*, 2013).

Rosenthal Fibers (RFs)

Overaccumulation of the GFAP protein produces protein aggregates that vary in size, structure, and density. These aggregates, called Rosenthal fibers (RFs), consist of intermediate filaments, GFAP protein, vimentin, synemin, alpha-B-crystallin, heat shock protein, plectin, and cyclin D2 (Heaven *et al.*, 2016) (*Figure 1*). The multi-component RFs disrupt astrocyte (glial cell) function and cytoskeletal orientation (Sosunov *et al.*, 2017). They do so by arresting mitosis in astrocytes, preventing cells from performing cytokinesis and duplicating (Sosunov *et al.*, 2017). If glial cells do not properly divide and proliferate, this causes disruption to myelination processes in the CNS. Many of symptoms reported in individuals with AxD are a result of this demyelination (Sosunov *et al.*, 2017).

Studies show that these astrocytic protein aggregates, called Rosenthal fibers, are strongly correlated with the amount of mutated GFAP protein expression and the length of disease course (Hagemann *et al.*, 2006). Current mouse models show that mice at one-month of age with AxD had fewer and smaller Rosenthal fibers in the CNS (Sosunov *et al.*, 2017). In comparison, mice at one-year of age with AxD had a greater quantity and larger RFs in the CNS (Sosunov *et al.*, 2017). Thus, a longer disease course is associated with increased neural pathology and associated disease severity.

Current therapies in development aim to suppress the faulty *GFAP* gene from overproducing GFAP protein (Hagemann *et al.*, 2018). If GFAP protein production is inhibited, protein aggregation and RFs are diminished. Thus, damage to the CNS would be slowed. However, the question arises: what are the consequences of inhibiting GFAP protein expression in the human body? Although doing so would mitigate the effects of AxD, will a lack of GFAP affect the body in unforeseen ways? Such inquiries are important to consider in therapy development, which will be discussed later in this paper.

Diagnosis of Alexander Disease

A definitive diagnosis of AxD requires molecular confirmation from genetic testing that indicates a positive mutation of the *GFAP* gene (Srivasta *et al.*, 1993). Prior to ordering a genetic test to confirm AxD, clinicians typically consider past medical history, symptoms at presentation, and radiology findings.

This diagnostic workflow is common for patients with heritable, monogenic disorders. Without full confidence that the *GFAP* gene contains a pathogenic mutation, it is possible to misdiagnose Alexander Disease. This is critical because AxD shares clinical presentations with other neurodegenerative diseases, such as Parkinson's Disease and Multiple Sclerosis (Costello *et al.*, 2009). Given that AxD becomes more severe with time, a misdiagnosis of Alexander Disease can have drastic implications– time is crucial to establish standard of care measures and ensure the best possible health outcome (Tavasoli *et al.*, 2017).

Radiology Findings

On magnetic resonance imaging (MRI), five distinct features are usually assessed (Graff-Radford *et al.*, 2013, for each of the five criteria below):

First, a frontal predominance of white matter shown by T2 hyperintensity and T1 hypointensity (*Figure 2*)

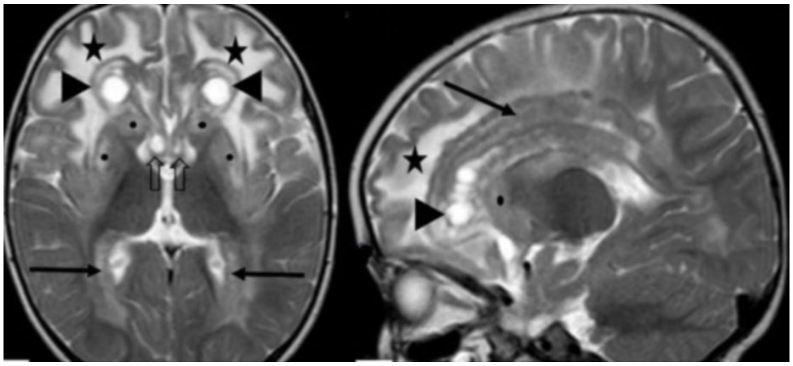

Figure 2. T2 white matter hyperintensities in the front parietal lobes (left) and anterior temporal lobes (right), with extension into the occipital lobes. (Dlamini and Plessis, 2016)

Second, a periventricular rim of T2 hypointensity and T1 hyperintensity (*Figure 3*)

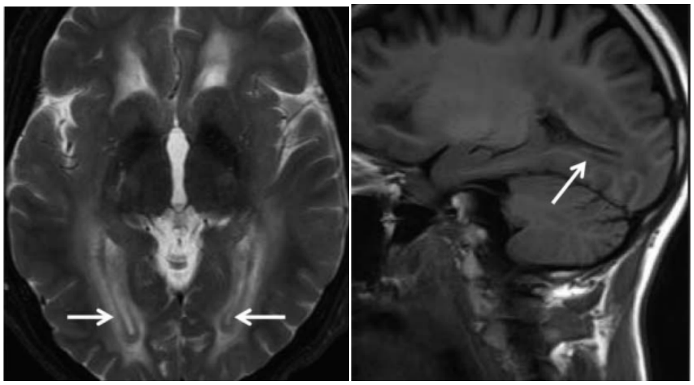

Figure 3. Pentriventricular T2 hypointensity (left), Petriventricular T1 hyperintensity (right). (Graff-Radford *et al.*, 2013)

Third, abnormalities of the basal ganglia and thalami evidenced by swelling and/or increased signal intensity on T2-weighted MRI. Atrophy with an abnormal signal intensity on T2-weighted images (*Figure 4*)

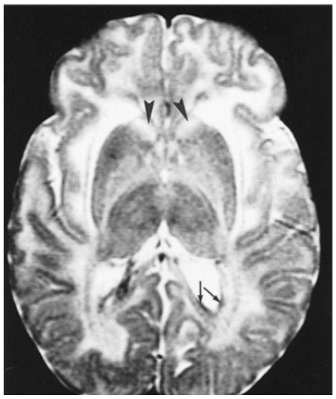

Figure 4. Abnormally high signal in the basal ganglia and thalamus. (Knaap *et al.*, 2001)

Fourth, the brain stem displays an atypical T2 signal (*Figure 5*)

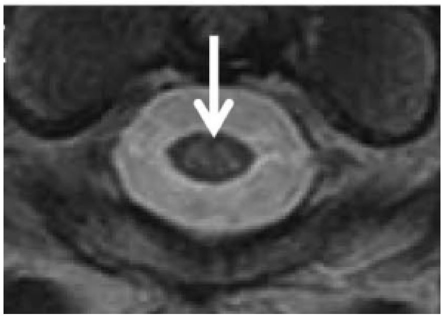

Figure 5. T2-weighted images showing an area of signal change and spinal cord atrophy. (Graff-Radford *et al.*, 2013)

Fifth, contrast enhancement of selected structures. When these collective abnormal features are presented on an MRI scan, AxD is strongly indicated on a clinician's differential diagnosis. However, to achieve a confirmed diagnosis of AxD, the individual must have a confirmed pathogenic *GFAP* mutation (Srivasta *et al.*, 1993).

Genetic Testing

To determine if an individual has a confirmed diagnosis of AxD, doctors order molecular genetic testing to sequence specific segments of a patient's genetic information (Srivasta *et al.*, 1993). Generally, when testing for Alexander Disease, doctors either use (1) gene-targeted testing to identify a mutation on the *GFAP* gene or (2) comprehensive genomic testing to scan for abnormalities in the complete exome or genome (Srivasta *et al.*, 1993). The choice between these two methods depends on the phenotype of the individual (Srivasta *et al.*,1993).

When a patient has several clear phenotypic indicators (i.e., symptoms) of AxD, geneticists might show preference for gene-targeted testing (Srivasta *et al.*, 1993). In this case, solely the *GFAP* gene is tested for a mutation. In contrast, when patients show symptoms characteristic of several different diseases and a diagnosis of AxD is unclear, geneticists might prefer a comprehensive genomic test, such as exome or genome sequencing (Srivasta *et al.*, 1993). Whole genome sequencing (WGS) tests both intronic (noncoding) and exonic (coding) sequences from the DNA, while whole exome sequencing (WES) tests the protein-coding genes within the exons (Belkadi, 2015). There are various factors that geneticists use to determine the appropriate test, but one strategy is to begin with WES and then escalate to WGS, if needed (Belkadi, 2015).

If a pathogenic *GFAP* mutation appears on testing, families can elect to determine the mode of inheritance for this mutation. In a Duo or Trio test, either one parent or both parents also test their DNA sequences to determine if a pathogenic mutation is inherited or *de novo* (Messing, 2018).

It is notable that even though *GFAP* mutations are the primary cause behind Alexander Disease, several reported AxD cases lack a *GFAP* mutation (Brenner *et al.*, 2001). In these cases, the causes of AxD remain unknown. Therefore, our scientific understanding of the molecular and biochemical markers involved in AxD is not fully understood and must evolve as new technologies emerge and advance the field.

Key Diagnostic Categories of AxD

There are four key diagnostic categories of AxD that are grouped based on the onset of symptoms: (1) the neonatal stage (consisting of the first month of life), (2) the infantile stage, (3) the juvenile stage, and (4) the adult stage (Kuhn and Cascella, 2022). Each category is characterized by slightly different clinical presentations and symptoms.

The most extreme of the four is the neonatal form. The most common symptoms include difficulty feeding, involuntary jerking, decreased muscle tone, developmental regression, megalencephaly (larger, heavier brain than average), seizures, hydrocephalus (accumulation of fluid in the brain), and cerebrospinal fluid (CSF) protein elevation (Medlineplus, Srivasta *et al.*, 1993). Those diagnosed with neonatal AxD commonly experience a rapid progression of symptoms, and their lives may be limited to the first two years of life (Springer *et al.*, 2000).

The infantile form is characterized by a more variable set of presentations yet shares key similarities to the neonatal form. Those diagnosed with the infantile form of AxD also experience a rapid regression, and their lives may be limited to the first four years of life (Srivasta *et al.*, 1993). The clinical presentations include the initial delay and plateauing of learning new skills, followed by losing the ability to perform such tasks altogether (NORD, 2017). Other symptoms include seizures, megalencephaly, loss of intellectual function, dysarthria (difficulty speaking), and failure to thrive (Pareyson *et al.*, 2008).

Those with the juvenile form generally present milder symptoms when compared to the neonatal and infantile forms, and the phenotype is significantly more variable (Srivasta *et al.*, 1993). The most common symptoms include developmental delay, seizures, intractable vomiting, scoliosis, and autonomic dysfunction (Srivasta *et al.*, 1993). Considering that symptoms are highly variable in this form, the life expectancy can range from months after a diagnosis to decades after a diagnosis (Messing, 2001).

Adult cases are known to have minimal symptoms, and some individuals live without knowing they have a neurologic condition. Generally, the symptoms at presentation include sleep disturbance, gait disturbance, hemiparesis/hemiplegia (partial paralysis) or quadriparesis/quadriplegia (complete paralysis), diplopia (double vision) or oculomotor abnormalities (Pareyson *et al.*, 2008). Similar to the juvenile form, the adult form is highly variable in its presentation. As a result, life expectancy of the adult form follows a similar trend of unpredictability (Srivasta *et al.*, 1993).

While grouping individuals with AxD can provide helpful diagnostic categories for potential therapeutic intervention, it remains difficult to predict precise phenotypic severity. Symptoms across the juvenile and adult stages are variable, and thus cannot be generalized for all individuals (Ozkaya *et al.*, 2012). There are instances when individuals in the same diagnostic category experience very different presentations (Pareyson *et al.*, 2008). Under the current model of Alexander Disease classification, these examples cannot be well-explained. In contrast, neonatal and infantile forms haver greater classification success with the current model (Springer *et al.,* 2000). Most individuals diagnosed in these two categories experience similar symptoms and share comparable lifespans (Springer *et al.,* 2000).

Current Standard of Care

Although clinical trials testing the safety and efficacy of an AxD drug candidate are currently underway, as of right now, there is no commercially available, disease-modifying cure. The experimental drug (Zilganersen) is currently in Phase 3 of clinical trials (ION373), and the mechanism primarily works by reducing GFAP protein levels rather than addressing the genomic origin of the disease. (Hagemann *et al.,* 2018).

In a clinical environment, the current standard of care for AxD focuses on managing the symptoms in order to optimize quality of life and extend a patient's lifespan for as long as possible (Adang *et al.,* 2017). The most common methods used are seizure control, nutrition and weight management, and the maintenance of pulmonary function (Messing *et al.,* 2010). Physical and occupational therapy are also recommended to improve and maintain motor capabilities (Adang *et al.,* 2017).

Given that the current standard of care for individuals with AxD is limited, it is imperative that increased advocacy and attention be brought to the condition. As with other leukodystrophies, there are potential options being tested, and there is great promise in the field. Increased awareness can garner the attention and resources required to achieve research goals and find a cure. The rare disease space is unique, and all efforts to inspire more people to become involved are encouraged and appreciated.

Gene Therapies

The basic premise of gene therapy is to transfer genetic information to specific cells in affected individuals (Scheller and Krebsbach, 2009). Although seemingly straightforward, the process requires advanced technology, impeccable timing, and great accuracy.

It is important to distinguish the mechanism of action for gene therapy and acknowledge possible limitations to "curing" a disease. Some leukodystrophies (LDs), such as x-adrenoleukodystrophy (X-ALD), metachromatic leukodystrophy (MLD), and Krabbe disease (GLD), involve both the destruction of existing myelin sheaths and a lack of myelin production (Van der Knapp *et al.,* 2016). Myelin production is halted if there is a loss of oligodendrocytes and Schwann cells, myelin-producing cells of the central and peripheral nervous systems (Chen *et al.,* 2021). Different therapeutic mechanisms might be needed to 1) prevent the loss of existing myelin and to 2) recover myelin-producing function (Li *et al.,* 2018).

Whether the lack of myelin is due to acute/chronic demyelination or oligodendrocyte dysfunction, unmyelinated axons are left exposed and vulnerable to cellular degradation. Degradation is an irreversible process, and the loss of neural cells can hamper the efficacy of a therapeutic approach (Alizadeh *et al.,* 2015). The deterioration of the myelin sheath (a classic presentation of leukodystrophies) coupled with the diminished production of myelin (caused by oligodendrocyte loss) can make gene therapies less effective (Kutzelnigg and Lassmann, 2014). If there are fewer healthy axons in the CNS, the delivery of therapeutic genes can be disrupted.

To overcome these challenges, researchers must determine the ideal window within a disease course for therapy administration. In this window, axons would be healthy enough to tolerate a therapeutic drug (Matthes *et al.,* 2012). On the other hand, if gene therapy is used too late into a patient's disease progression, the therapeutic benefit can be significantly reduced, and the disease might continue its progression (Gordon-Lipkin and Fatemi, 2018)

Additionally, even if a gene therapy is administered at the ideal time and can successfully prevent myelin destruction, recovering myelin (remyelination) from oligodendrocyte precursor cells is complex and not possible in all circumstances (Villoslada and Martinez-Lapiscina, 2019). Thus, while a gene therapy might be able to stop the progression of a disease, it might not be able to recover function entirely. Functional recovery relies on remyelination, which is a complex process that becomes more difficult as the brain ages and accumulates neural injury. Recovery and remyelination approaches are still being studied in the field (Klistorner and Barnett, 2021). These are critical limitations to consider in designing a therapeutic approach.

As mentioned, the extent of therapeutic benefit depends on one serious factor: age. In a fully matured brain (> 25 years), the remyelination process is nowhere near as efficient as it is in a developing brain (< 25 years) (Arain *et al.,* 2013). This can be credited to the concept of brain plasticity, in which neural connections are made and reprogrammed as one experiences stimuli in the world (Giedd *et al.,* 1999). Plasticity is responsible for recovery and regeneration, but this process becomes more complex and difficult with increasing age.

All things considered, if gene therapies are employed at the right time and in the right manner, affected individuals can experience positive health outcomes. Disease progression could slow, improving quality of life for many children and adults. However, due to limitations discussed above, it is crucial for the scientific community to experiment with additional mechanisms to find a cure AxD. One related approach, currently being tested in a clinical trial, uses antisense oligonucleotides.

Current Treatment Options

Alexander Disease was first described in 1949, and since then, the standard of care consists of symptom management and quality of life improvements (Messing *et al.,* 2010). This is because there is currently no disease-modifying treatment for AxD.

In recent years, a promising drug candidate (ION373 or Zilganersen) has entered into clinical trials and has shown much success in the battle against AxD (Anthony, 2022). Unlike the current options, this therapy is not another medicine to manage symptoms; rather, it acts to prevent the progression of AxD through periodic treatments that inhibit GFAP protein expression.

Zilganersen (ION373) is an antisense oligonucleotide (ASO). ASOs are synthetic, single-stranded oligodeoxynucleotides that are able to alter messenger ribonucleic acid (mRNA) in order to modify the expression of toxic protein, promote the expression of functional protein, or modify the structure of a protein to improve function (Amanat *et al.,* 2022). Since it is commonly accepted among researchers and physicians that GFAP protein expression is correlated with AxD presentation and severity, ASO therapy can be used to target the mRNA of GFAP proteins and inhibit production (Amanat *et al.,* 2022). Thus, the accumulation of RFs and the consequent demyelination of the CNS could be halted if GFAP protein expression in the therapeutic group is similar enough to GFAP protein expression in individuals who do not have a mutated *GFAP* gene (wild-type group).

Mechanism of ASO-Targeted Therapy

First, the synthetic antisense oligonucleotide is designed to be complementary to the mRNA segment that it will bind to (Hill and Meisler, 2021). In the case of Zilganersen (ION373), the mRNA coding strand for the GFAP protein is the target.

Second, the ASO is injected into the particular area of interest (Southwell *et al.,* 2012). Zilganersen (ION373) is administered intrathecally, into the spinal canal, so the drug can absorb into cerebrospinal fluid within the CNS. This injection type avoids the blood-brain barrier, a protective layer of the brain that often prevents the passage of drugs and toxins into the CNS (Soderquist and Mahoney, 2010). By injecting intrathecally, the drug can efficiently target cells in the CNS.

Third, the ASO binds to the complementary mRNA coding strand through base-pairing interactions (Hill and Meisler, 2021).

The ASO inhibits protein expression by preventing transfer ribonucleic acid (tRNA) from binding to the mRNA strand and completing the translation process (Hill and Meisler, 2021). If tRNA cannot bind to the mRNA, the amino acid sequence cannot be built, and the protein cannot be created. In the case of AxD, the ideal scenario suppresses GFAP protein expression, and the amount of GFAP protein in the CNS mirrors wild-type expression.

Lastly, in the ideal scenario, if the drug works as designed and GFAP accumulation is corrected, an affected individual will achieve improvement from baseline as identified by the study's primary and secondary outcome measures. For the ION373 Phase 1-3 clinical trial, a primary measure of efficacy involves improvement from baseline to Week 61 on the 10-Meter Walk Test (10-MWT) (Ionis Pharmaceuticals). Secondary measures of efficacy include various improvements to fine and gross motor skills, subjective quality of life, symptoms, and GFAP protein levels in the CSF (Ionis Pharmaceuticals).

Advantages of ASO-Targeted Therapy

ASO-targeted therapy is an innovative method to provide patients with effective therapeutic options that do not directly alter the genome. The process of developing and administering ASOs is relatively straightforward (Walters *et al.,* 2016). Unlike other complex drugs, the synthesis of ASOs involves creating complementary strands of RNA to bind to a targeted site on an individual's coding mRNA strand (Hill and Meisler, 2021).

Furthermore, ASOs operate with great precision (Carrol *et al.,* 2011). The synthetic strands created can be tailored for exact mRNA segments in a patient's genome which allows for customized therapeutic options that can be specific to a particular disease sequence (Carrol *et al.,* 2011). For Alexander Disease, the mRNA coding strand for the GFAP protein is exclusively targeted, while for Duchenne Muscular Dystrophy (DMD), on the other hand, the mRNA encoding dystrophin protein is targeted (Scoles *et al.,* 2019).

Also, because ASO-targeted therapy has high mRNA specificity, this mechanism limits off-target effects, which can be primary concerns for other therapeutic options, such as CRISPR/Cas9 gene editing tools (Walters *et al.,* 2016). Off-site effects are unintended consequences of silencing certain protein encoding domains– they should be avoided to ensure efficacy and safety of the therapeutic candidate (Walters *et al.,* 2016). In ASO-targeted therapy, only one RNA segment is exactly complementary and more often than not, the desired effect is achieved once the ASO properly binds with the target RNA.

Challenges to ASO-Targeted Therapy

Even though ASOs are fairly easy to produce, they are quite expensive, as with other early-stage therapeutics (Kuijper *et al.,* 2020). If Zilganersen (ION373) is successful in clinical trial and approved for commercial market, there may be a financial barrier preventing those with unfavorable socioeconomic circumstances from receiving ASO treatment. I believe that therapies should be accessible for all individuals who are affected by AxD, regardless of their circumstances, and it is my hope that any future commercially available treatments will be affordable for all.

In addition, as discussed above, the precision of ASOs greatly minimize off-target effects but do not entirely eliminate them (Kuijper *et al.,* 2020). While targeting specific strands of RNA, unintended side effects can result. For example, when considering AxD, suppressing the GFAP protein would mitigate the symptoms of AxD. However, scientists must consider that additional concerns may arise for individuals who lack cellular tools for GFAP expression. Or, if the wrong protein is suppressed, there can be profound impacts on the body's function, and the desired effect would not be achieved.

Lastly, since ASOs are not a gene therapy, the drug must be administered multiple times, as this therapy is not a permanent improvement. This can be a disadvantage because patients will have to undergo routine, invasive treatments with risks for unwanted consequences. For example, considering ION373, undergoing multiple intrathecal injections can introduce continuous risk for infections, bleeding, and nerve damage (Tunkel and Pradhan, 2002). This risk is compounded considering that such injections must happen multiple times over the course of a patient's treatment.

Future Therapeutic Recommendation

Current approaches use intrathecal injections, but there are several risks to administering a drug into the spinal canal, including CSF leak, obstruction to CSF flow, and infection (Delhaas and Huygen, 2020). To eliminate the risk that intrathecal injections pose in ASO-targeted therapy, an alternative route of administration to consider is intravenous injections (Delhaas and Huygen, 2020). Such injections would not enter the nervous system directly; instead, they would travel to the CNS by the blood, resulting in an alternative delivery of the ASO.

Intravenous injections are sometimes not considered favorably because of the inconvenience of delivering a drug through the blood-brain barrier (Daneman, 2015). This semi-permeable membrane surroundings the brain, establishing a barrier that closely regulates which substances are moved between the blood and the brain (Daneman, 2015). Therefore, if ASOs are delivered without any modifications through the bloodstream, they would have no effect because the blood-brain barrier would prevent entry into the CNS. Taking this into consideration, scientists can use the knowledge of current therapeutic candidates, like the Zilganersen (ION373) ASO, and synthesize a new type of treatment, such as a heteroduplex oligonucleotide (HDO) (Kuwahara *et al.,* 2018). HDOs are very similar to ASOs with the added feature of being able to cross the blood-brain barrier (Kuwahara *et al.,* 2018). Since scientists have already identified the mRNA sequence codes of the GFAP protein, creating an HDO similar to the present ASO should be considered. I propose that future experimentation, with these points in mind, would be advantageous in therapeutic development for Alexander Disease.

Conclusion

In recent years, scientists and researchers have achieved great progress in understanding the complexities of Alexander Disease; however, work is far from over in the search for a cure. There still is no commercially approved, disease-modifying treatment available to prevent the progression of AxD. Therefore, it is vital to continue studying potential therapeutic options that can effectively treat this rare condition. This paper offers an innovative suggestion of using an intravenous heteroduplex oligonucleotide to address evolving therapeutic needs. Rare diseases may not garner as much interest as many other conditions, but they are no less important. This review of Alexander Disease aims to provide an accessible glimpse into the rare disease space of neurodegenerative diseases and the innovation that continues to drive the field forward.

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