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Short Communication

Current Emerging Therapy for Amyloidosis Neuropathy

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ABSTRACT

Peripheral neuropathy is a type of neurological disorder in which patients with complex inherited neurological defects present significant phenotype in the peripheral nervous system. Hereditary amyloidogenic transthyretin (hATTR) neuropathy is typical polyneuropathy caused by single-nucleotide variants in the gene encoding transthyretin (TTR) and leads to transthyretin misfolding and systemic deposition of amyloid. One of the clinical hallmarks of hATTR neuropathy is polyneuropathy of the destruction of the somatic and autonomic peripheral nervous system, leading to loss of autonomy. Progressive amyloid accumulation also causes multi-organ dysfunction and death. There are many therapeutics that have been proposed and developed in these years. These therapies aim to reduce or eliminate hATTR from the plasma, stabilize the hATTR to prevent deposition, and dissolute the amyloid misfolding matrix. Recently, gene therapy strategy is being deployed to treat recessive genetic disorders by eliminating the expression of the mutated genes. Thus, gene-silencing approaches have been used to manage this amyloidosis neuropathy in the broad stages and produce some degree of improvement of this disease. Food and Drug Administration (FDA) approved Inotersen (an antisense oligonucleotide (ASO)) and patisiran (a small interfering ribonucleic acid (siRNA) for the treatment of hATTR polyneuropathy to suppress hATTR expression. Inotersen, a 2'-O-methoxyethylmodified ASO, which acts by reducing the production of transthyretin, and has been demonstrated to improve the quality of life in early hereditary transthyretin amyloidosis polyneuropathy. I here focus on the RNA-targeted therapy with particular emphasis on the molecular mechanisms by which antisense oligonucleotide can be designed to modulate transthyretin RNA function for being a novel therapy for hereditary amyloidosis neuropathy.

Keywords
Peripheral neuropathy; Amyloidosis; Antisense oligonucleotide (ASO).

PEREPHERAL NEUROPATHY

Peripheral neuropathy is a typical phenotype based on the problems that happened at the root of the damaged nerve. Over 50% of peripheral neuropathy are inherited neurological disorders caused by several numbers of causative genes, and it usually comes with different levels of phenotype. Among the peripheral neuropathy, polyneuropathy accounts for the massive amount of cases. It occurs when there are multiple nerves throughout your body present malfunction. It has been known that several reasons may cause polyneuropathy, including exposure to specific toxic or poor nutrition, or due to a side effect from diseases. The most common symptoms of polyneuropathy are tingling, numbness, loss of sensation, and a burning sensation in the extremities. One of the most severe polyneuropathies called guillain-barre syndrome (GBS), a rare disease that strikes suddenly when the immune system attacks nerves. Symptoms tend to appear quickly and worsen rapidly, sometimes leading to paralysis.[1] Currently, around 20-30% of Americans suffering from peripheral neuropathy. Although the influence is broadly cross all ages, the older adults are at increased risk. According to the statistic of peripheral neuropathy, there are 30% of patients with diabetic peripheral neuropathy (DPN),[2] 30% of patients with chemotherapy-induced peripheral neuropathy (CIPN),[3] and around 35% of patients with the human immunodeficiency virus-induced peripheral neuropathy.[4]

FAMILIAL AMYLOID POLYNEUROPATHY

Among different factors induced peripheral neuropathy, familial amyloid polyneuropathy (FAP) is a peculiar form of peripheral neuropathy, induced by a genetic mutation. FAP usually leads

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to progressive lower extremity weakness and loss of pain sensation.[5,6] It is an autosomal dominant disorder characterized by the deposition of amyloid in the peripheral nerve system. Amyloidosis occurs due to the misfolded extracellular protein generating amyloid fibrils that are deposited into different tissues. The deposition of *transthyretin (TTR)* amyloid fibrils in tissue is known as amyloidosis transthyretin (ATTR).[7] The cause of hATTR is due to a mutation that occurred in the TTR gene. The main feature is polyneuropathy (hATTR-PN) or cardiomyopathy (hATTR-CM). There are over 150 reported mutations of the *TTR* gene.[7] The most common variation is Val30Met, where valine is replaced by methionine at position 30 (148G to A). The Val30Met variation is endemic in Portugal, Sweden, and Japan.[8] Although polyneuropathy is a common presentation, initial symptoms range from chronic inflammatory demyelinating polyneuropathy (CIPD), cardiomyopathy, carpal tunnel syndrome, lumbar canal stenosis, chronic digestive disease, and idiopathic polyneuropathy.[7] The global prevalence of hATTR amyloidosis was estimated round 10,000, with estimates ranging from 5,000 to 40,000 affected individuals. This estimation was based on the prevalence in seven core countries. However, the number might be an underestimate due to the phenotypic variability of hATTR.[7]

Hereditary transthyretin amyloidosis (hATTR) is a devastating polyneuropathy due to amyloid accumulation in the peripheral nervous system. Initial therapy for hATTR-PN is symptomatic. The pain from the polyneuropathy is often severe and debilitating. Treatment of hATTR includes removing the source of mutant TTR using small molecules, Diflunisal[9] and Tafamidis,[10] reducing the amount of ATTR deposition using doxycycline[11] and tauroursodeoxycholic acid (TUDCA),[12,13] or genetic therapy with *TTR* oligonucleotides to reduce the production of both mutated and Wild-type (WT) TTR.[14] Both tafamidis and diflunisal are selective TTR stabilizers has been approved for the treatment of FAP patients with early-onset polyneuropathy to delay neurological impairment.[9,10] Doxycycline has shown its effect *in vivo* in ATTR Val30Mat transgenic mice.[11] TUDCA, a natural compound, is a potent antioxidant agent since it reduces cytotoxicity in neurodegenerative diseases. Also, TUDCA treatment significant decreased the amount of TTR toxic aggregates.[12]

EMERGING THERAPY OF AMYLOIDOSIS NEUROPATHY

In 2018, two ribonucleic acid (RNA)-based therapeutic showed positive results in the clinical trial III and lead to Food and Drug Administration (FDA) approval route. The first drug is Patisiran, an RNA interference drug developed and marketed by Alnylam. The other drug is Inotersen, a 2'-O-methoxyethyl-modified antisense oligonucleotide, which acts by reducing the production of transthyretin, developed by Ionis Pharmaceuticals.[15,16]

Ribonucleic acid therapy is one of the updated technology for the therapeutic of hATTR-PN. RNA interference (RNAi) or small interfering RNA (siRNA) targets the messenger RNA (mRNA) for further cleavage or inhibition of mRNA expression. RNAi is mediated by binding mRNA in the cytoplasm and leads to a degradation of mRNA by Dicer siRNA mechanism. Patisiran® (ALN-TTR02; Alnylam, Cambridge, MA, USA) is a siRNA encapsulated in a lipid nanoparticle delivered to intracellular compartments of hepatocytes using an intravenous infusion.[16] It binds to the 3'-UTR of mutant and WT TTR mRNA. FDA approved Patisiran in 2018.[16] In the phase III trial of Patisiran, there were 225 patients that were randomly assigned to receive Patisiran or placebo. In the Patisiran treated group, transthyretin level was rapidly reduced in the serum and sustained over 18-months. At the end-point, 56% of the patients who received Patisiran had an improvement compared to 4% improvement of the patients who received a placebo. However, 97% of the patients in each trial group reported adverse events.[16] Revusiran (Alnylam, Cambridge, MA, USA) is another siRNA compound that conjugated with N-acetylgalactosamine and given subcutaneously (SC) for hATTR-CM. However, the clinical trial was halted due to an imbalance of mortality in the treatment compared to controls.[17]

Another updated technology for the therapeutic effect of hATTR-PN is ASO therapy. ASO therapy was developed in the late 1970s. Due to the massive negative polarity, ASOs were challenging to cross the cell membranes. Another challenging part of ASOs is immune responses trigger. These challenges were addressed recently by chemical modification on the ribose backbone with phosphorothioate (PS), which facilitated cell update and beneficial for pharmacokinetics (PKs) broadly *via* binding to the cell surface and intraocular proteins.[18] Additional 2'-O-methoxyethyl (2'-MOE) modifications also improve PKs and the binding affinity to plasma protein, which would allow the stability of antisense oligonucleotides (ASOs) against nucleases. Besides, 2'-MOE modification also increases the potency by improving the binding affinity of complementary hybridization. Moreover, the MOE modification enhances the safety profile *via* eliminating the nonspecific binding inducing toxicities.[19] The protein expression can be altered using two different mechanisms. The first mechanism is enzymatic RNA degradation using ribonuclease H (RNase H), which is an endonuclease in the nucleus. RNase H can recognize the RNA/deoxyribonucleic acid (DNA) heteroduplex and catalyzes the cleavage of RNA. That would reduce the expression of mutant and wild-type protein. Also, RNase H can prevent RNA from attaching to the ribosome to block protein transcription. The second mechanism is targeting on RNA splicing. ASO can bind to the pre-mature RNA to alter the RNA splicing without triggering RNA degradation. This exon-skipping mechanism can inhibit translation to reduce the production of the toxic protein, enhance the translation to restore the deficient protein, or obstruct interactions to modify the functional effect of the protein.[20]

Inotersen™ (Ionis, Carlsbad, CA, USA) is the most potent ASO target to TTR 3'-UTR mRNA that identified as a hepatic TTR inhibitor. Inotersen consists of 20 bases full-PS chimeric ASO with five 2'-MOE-modified ribonucleotides at each terminus, and a central region of ten 2'-deoxynucleotide residues (a 5-10-5 gapmer structure).[21] It binds to the mRNA with complementary base pairing mimicking the DNA/RNA complex and then recruits RNaseH1-mediated degradation of TTR mRNA to prevent mutant TTR production. Thus, the formation of TTR amyloid fibril deposits will be reduced and slows disease progression effectively.

hATTR is a devastating disorder with death, and it often occurs in patients around the age of 30. The inability of the previous small molecule to prevent hATTR progression led to the discovery of RNA and ASO therapeutic. Especially, Inotersen™, an ASO can be given once a week. Inotersen becomes available for hATTR to prevent disease progression and improve quality of life for the treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults in 2018. The study investigated 172 patients (112 patients were in the Inotersen group, and 60 patients were in the placebo group). Patients received three subcutaneous injections to achieve steady-state drug levels, followed by a once-weekly dose for the next 64-weeks. At the end-point, pre-specified sensitivity analyses showed a robust and beneficial Inotersen treatment effect. Further study showed 36% of the patients in the Inotersen group had an improvement in the mNIS+7, and 50% of the patients had an increase in the Norfolk quality of life questionnaire–diabetic neuropathy (QOL-DN) score. However, there were five deaths in the Inotersen group. The most severe adverse events in the Inotersen group were glomerulonephritis (3%) and thrombocytopenia (3%).[15] Although Inotersen showed a significant improvement, it doesn't cross the blood-brain barrier to the reach the central nervous system. Thus, it would not be effective in hATTR patients with predominant retinal or leptomeningeal symptoms. The delivery of the ASO in patients may be performed intravitreally and intrathecally to address these issues.[20,22]

CONCLUSION

Currently, there have been a couple of treatment options for hATTR patients. Primarily, RNA therapy (patisiran) and ASO therapy (Inotersen™) represent a significant advance in the field of amyloidosis. The unique mechanisms of action of inotersen™ and patisiran® overcome many limitations of other treatments. Both are efficacious in hATTR patients with early- and late-onset stages. Besides, both improve and slow the neuropathy progression. Although RNA therapy and ASO therapy are emerging treatments for peripheral neuropathy and other neurological disorders, formulation, dosing, and safety monitoring are different than conventional medicines. Thus, additional research is still necessary to understand the detail mechanism and effectiveness of these pioneer therapies when patients with hATTR receive these emerging therapies. As these pioneering and emerging therapies expand, the prospect for patients is becoming more promising, offering hope for a debilitating and life-threatening disease.

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