Innovative Treatment Approaches for Inherited Neuromuscular Disorders

Layla Southcombe
Editorial Assistant

INHERITED neuromuscular disorders (NMD) provide a great challenge to the treating clinician owing to their characteristically chronic and progressive nature. Historically, it has been difficult to find effective treatments for these disorders because their pathogenesis is of a genetic nature. Over the last decades, however, gene and RNA-based therapies have gained enormous interest, leading to a collection of such therapeutics now being approved for conditions affecting a variety of bodily systems. In a session at the 2020 European Academy of Neurology (EAN) Virtual Meeting, four experts in NMD discussed the rapid progression in new pharmacological technologies that have occurred as a result of improved understanding of pathophysiological and genetic mechanisms of NMD.

GENE THERAPEUTIC APPROACHES FOR NEUROMUSCULAR DISORDERS

During the first presentation, Dr Teresinhaas Evangelista, Hôpital Pitié-Salpêtrière, Paris, France, introduced the concept of a gene therapy as a biological medicinal product containing RNA, capable of inducing the regulation, replacement, addition, or deletion of a genetic sequence. Two main delivery systems for gene therapies currently exist: 1) *in vivo*, in which the gene is introduced directly into the patient; and 2) *ex vivo*, in which cells are isolated from the patient, genetically modified, and then reintroduced back into the patient. *In vivo* gene therapy is commonly used for monogenic disorders in post-mitotic tissues, and hence is the popular choice for NMD, Dr Evangelista explained. Using engineered plasmids or viruses, copies of functional genes can be delivered into patients with genetic diseases, whereby the vector will produce a functional version of the missing protein. Gene expression can also be modulated by small synthetic fragments of single-stranded nucleic acid sequences called antisense oligonucleotides (ASO), which can be administered without the use of a vector. ASO can be designed to either promote exon skipping or splicing of precursor mRNA, or to promote degradation of mRNA for gene knockdown. Dr Evangelista concluded her presentation by highlighting current hurdles that exist for these therapeutics from a clinical standpoint, namely that "gene therapy approaches are presumably irreversible, potentially providing sustained benefits but also raising the spectre of long-term untoward effects."

"Gene therapy approaches are presumably irreversible, potentially providing sustained benefits but also raising the spectre of long-term untoward effects"

THE EVOLVING LANDSCAPE OF RNA-BASED THERAPIES

Antisense Oligonucleotides

Prof Giuseppe Vita, University of Messina and NeMO Sud Clinical Centre, Messina, Italy, discussed the mechanism of actions and summarised key clinical data for innovative ASO therapies for NMD that have reached the market in recent years. Spinal muscular atrophy (SMA) is a rare disorder caused by a loss-of-function mutation in the *SMN1* gene, which results in the inability to code the survival motor neuron (SMN) protein and presents as the loss of motor neurons and progressive muscle wasting. *SMN2* is a gene that is also capable of producing SMN, but it differs to *SMN1* by a single nucleotide substitution that leads to the exclusion of exon 7, rendering 80–90% of its transcripts to be truncated, unstable, and of no biological function, whereas the remaining 10–20% are still functional. Dr Vita explained that the ASO drug nusinersen can bind to *SMN2* precursor mRNA and thereby modify the splicing of it, functionally converting it to *SMN1* and therefore increasing the production of the full-length SMN protein. Initial clinical trials were prematurely halted because the drug showed clear benefit to patients, with real-world data also reflecting this. After 6 months of treatment, an increase of more than 2 points in Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND; an evaluation of motor skills) occurred in 56% of patients, and an increase of more than 4 points occurred in 28% of patients older than 2 years and 30% of patients older than 10 years.[1]

Eteplirsen is another ASO that has been approved by the U.S. Food and Drug Administration (FDA) to treat an NMD, but its target and action on RNA differs to that of nusinersen. Duchenne muscular dystrophy (DMD) is characterised by progressive muscle weakness that manifests as a result of various mutations to the dystrophin gene, including the deletion of exon 51, which leads to a disruption of the reading frame. To counter this deletion, explained Dr Vita, eteplirsen binds to the mutated exon 51 so that when the gene is translated from the mature mRNA, the exon is skipped over and therefore the disrupted reading frame is restored, creating a truncated but functional dystrophin protein. Clinical trial data showed that eteplirsen stabilised the 6-Minute Walking Test (6MWT) initially, then improved scores after 48 weeks, versus 6MWT deterioration observed with placebo.[2] However, the European Medicines Agency (EMA) are yet to approve the therapy due to concerns over the robustness of the data. A dystrophin exon 53 skipping agent, golodirsen, was recently approved by the FDA for DMD, but again is yet to be approved by the EMA.

Hereditary transthyretin amyloidosis (hATTR) is a neurodegenerative disorder for which the pathogenesis can be one of more than 130 mutations of the *TTR* gene. Normal transthyretin (TTR) proteins bind to form tetramers, but mutations in the *TTR* gene interfere with this tetramer formation and stabilisation. As a result, the proteins misfold and exist as monomers, which aggregate to create fibrils that accumulate across the body, including the peripheral nerves, cardiac muscle, and kidneys. Inotersen is an ASO to TTR mRNA, which it selectively binds to trigger its degradation through RNAase H1, leading to the reduced production of TTR and thereby reducing the accumulation of the protein fibrils. A Phase I study demonstrated significant reductions in circulating TTR. In Phase III trials, inotersen demonstrated good efficacy, with significant reductions in the change in modified Neuropathy Impairment Score+7 (mNIS+7) and patient-reported Norfolk Quality of Life-Diabetic Neuropathy (QOL-DN) questionnaires seen at 14 months versus placebo.[3] Dr Vita added: "Inotersen is also effective in the cardiomyopathy, which is a clinical challenge of TTR amyloidosis. It is able to decrease left ventricular mass, interventricular septal thickness, and increase motor performance measured by 6MWT."[4] A recent open-label Phase III study confirmed that inotersen slows disease progression and reduces quality of life deterioration.

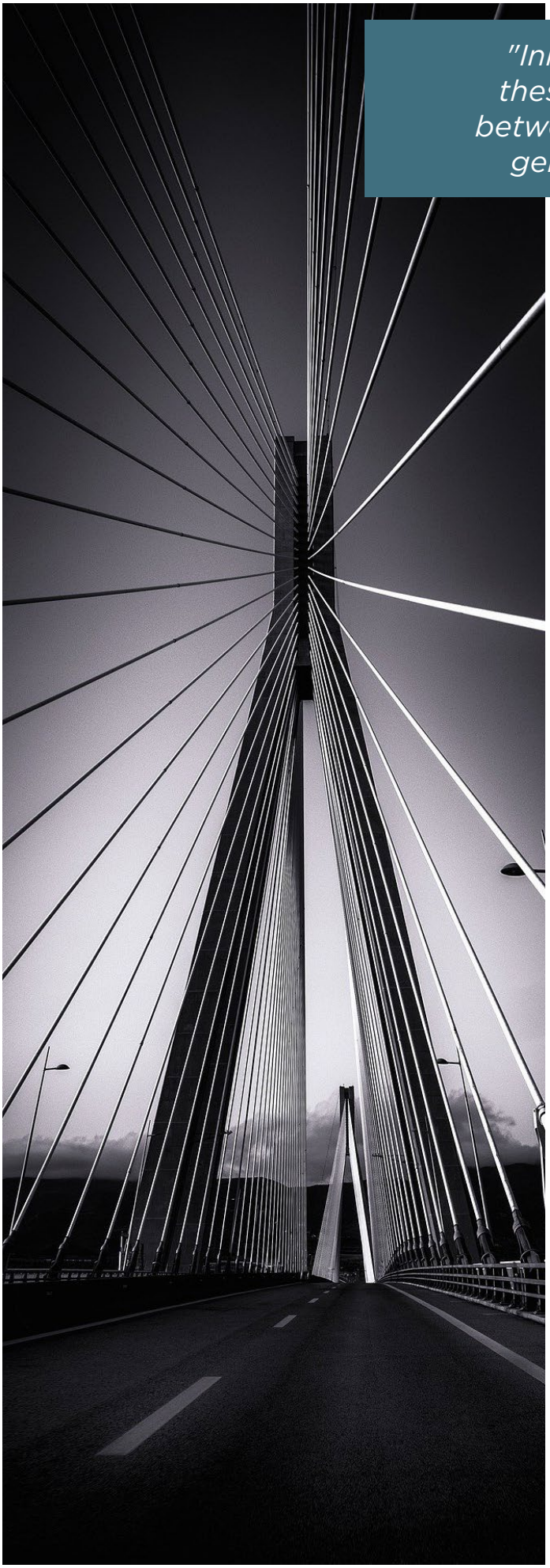
RNA Interference

Patisiran is another RNA therapy for hATTR that has shown remarkable Phase III results, and is the first small interfering RNA-based drug to receive approval from the FDA. Utilising the endogenous RNA interference pathway, patisiran selectively binds to the TTR mRNA, triggering its degradation and therefore suppresses its translation and production of the TTR protein. In the Phase III APOLLO trial, patisiran was able to induce a mean maximum serum TTR reduction of up to 90% over 18 months versus placebo.[5] There was a stabilisation and an unexpected improvement in mNIS+7 and quality of life over 18 months of patisiran versus placebo, potentially suggesting that it halts and possibly reverses the progression of amyloidotic polyneuropathy.[6] While both inotersen and patisiran have shown significant reductions in circulating TTR by targeting the liver, where 85% of TTR is produced, neither of the therapies can cross the blood–brain barrier (BBB), an important factor for a complete resolution of symptoms as 12% of TTR is synthesised in the brain. Strategies to allow such molecules to cross the BBB are currently under investigation, including intrathecal administration, viral vectors, and agents that temporarily disrupt the BBB, such as mannitol and bradykinin.

TOWARDS A BETTER UNDERSTANDING OF ENZYME REPLACEMENT THERAPIES

Inborn errors of metabolism (IEM) are disorders that usually occur from defects in enzymes involved in metabolic pathways. Such defects stop a specific substrate being converted into its product, for which symptoms can occur because of either an accumulation of the substrate and/or a deficiency of the product. Enzyme replacement therapy (ERT) is a treatment that aims to replace the deficient enzyme so that the metabolic process can occur. Although individually rare, more than 1,000 different IEM are thought to exist, meaning that collectively they are common and are estimated to affect between one in seven and one in 10 of the population.

Dr Mark Roberts, Salford Royal NHS Foundation Trust, Salford, UK, showcased the use of ERT in IEM with Pompe disease, a rare genetic disorder caused by a mutation in the gene encoding α-glucosidase, an enzyme that breaks down glycogen in the lysosome to release glucose back into the cytosol. This enzyme deficiency causes accumulation of glycogen in the lysosome, which leads to the lysosome rupturing, releasing their hydrolytic, and therefore potentially destructive, enzymes into the cytosol. The severity of this disease's progression means that infants often die at just 8 months old, despite clinical presentations being well defined and



"Innovative adjustments such as these are likely to bridge the gap between today and the sought-after genetic therapies of tomorrow"

including significant weakness, head lag, and hypotonia. Adults can also present with Pompe disease due to the variability in levels of enzyme deficiency. Myozyme is a humanised analogue of α-glucosidase that binds to the M6P receptor on cells and is internalised by endocytosis before being trafficked to the lysosomes where it degrades glycogen, preventing accumulation, and releases glucose back into the cytosol. Myozyme was approved by the FDA and EMA following the results of an open-label study in which 18/18 infants treated with myozyme were still alive at 18 months of age versus just 1/62 in the untreated controls.[7] Limitations to myozyme do exist however: in many infants, immune reactions to ERT can occur and therefore medications, often a cocktail of drugs including rituximab, are needed to induce immunotolerance; myozyme does not cross the BBB, so symptoms such as deafness and cognitive dysfunction are still manifested; and for the adult patients, the progression of disease is only delayed and not entirely halted, which Dr Roberts stated is a way of buying essential time for patients until new therapeutics, including gene therapies, are discovered.

A very-high dose of myozyme is required to elicit a response, owing to just 1% of the enzymes reaching the lysosomes. To address this shortfall, NeoGAA, an enhanced enzyme with increased binding to the M6P receptor, has been developed and was successful in Phase I and II trials and is now in Phase III, in which it is being compared to myozyme. Another enhanced enzyme is ATB200, which, in addition to increased M6P binding, has additional glycans to enhance entry into the cells. ATB200 is also administered with a chaperone, which has been shown to stabilise the ERT in the blood and maintain catalytic activity, increasing delivery of active enzyme to the lysosome. Innovative adjustments such as these are likely to bridge the gap between today and the sought-after genetic therapies of tomorrow, studies for which are likely to start soon.

THE ROLE OF SMALL MOLECULE APPROACHES TREATING INHERITED NEUROMUSCULAR DISORDERS

The therapeutic pipeline for countless diseases has been flooded with biologics and RNA therapies, but during her talk, Dr Maria Molnar, Semmelweis University, Budapest, Hungary, reminded the audience that small molecules are still a very promising therapeutic approach for inherited NMD, and represent around 40% of newly approved orphan drugs. Small molecules dominate the field because of certain characteristics, such as their ability to be designed to target and reach intracellular targets and cross the BBB, which biologics are unable to achieve; they can be orally administered; and are able to be distributed via the blood circulation compared with the blood and lymphatic system seen in biologics, meaning that peak concentrations can be reached faster. However, drawbacks to using small molecules do exist, such as an increased number of off-target sites and more drug–drug interactions compared with biologics.

Repurposing already approved drugs can be a resourceful approach to finding a therapeutic that can ameliorate symptoms of rare diseases

A small molecule that has exemplified the targeting of RNA as a therapeutic approach is ataluren, which is indicated for DMD caused by nonsense mutations in the dystrophin gene. Ataluren makes ribosomes less sensitive to the premature stop codons, which allows for the readthrough and the synthesis of the full-length, functional protein. Risdiplam is indicated for SMA and works in a similar manner to nusinersen by binding to the *SMN2* precursor mRNA and thereby modifying the splicing of *SMN2* to include exon 7 and increase the production of functional and stable SMN proteins. One key difference between the two therapies is that risiplam can cross the BBB.

Since the number of patients affected by a single genetic disease is very low, the incredible cost to research and develop a drug means that pharmaceutical companies can be hesitant to investigate potential therapeutics. Repurposing already approved drugs can be a resourceful approach to finding a therapeutic that can ameliorate symptoms of rare diseases. Among such repurposed drugs include mexiletine, a sodium channel blocker that was developed as an antiarrhythmic, to reduce myotonias; deflazacort, a glucocorticoid that has numerous applications, can be used in DMD to improve muscle strength in the short term; and PXT3003, a combination of baclofen, naltrexone, and sorbitol, is being investigated for use in Charcot-Marie-Tooth Disease Type 1A.

SUMMARY

This session from the 2020 EAN Virtual Meeting showcased that the current and prospective treatment landscape for inherited NMD is one full of hope and innovation. Interest in and development of RNA therapies is thriving, and many have proven to be the out-reaching hand patients have been grasping for. The price tags that accompany these innovative therapies, however, can severely limit patient access and is a paramount challenge that needs to be addressed to secure these lifelines for patients. As RNA therapies and biologics grow exponentially, the small molecules should not be forgotten, as they continue to demonstrate their value in the NMD field.

References

1. Pane M et al. Nusinersen in Type 1 SMA infants, children and young adults: preliminary results on motor function. Neuromuscul Disord. 2018;28(7):582-5.
2. Charleston JS et al. Eteplirsen treatment for Duchenne muscular dystrophy: exon skipping and dystrophin production. Neurology. 2018;90(24):e2146-54.
3. Benson MD et al. Inotersen treatment for patients with hereditary transthyretin amyloidosis. N Engl J Med. 2018;379(1):22-31.
4. Dasgupta NR et al. Inotersen therapy of transthyretin amyloid cardiomyopathy. Amyloid. 2020;27(1):52-8.
5. Coelho T et al. Transthyretin reduction with patisiran in the APOLLO Phase 3 study. ICNMD, Vienna, Austria, 6-10 July 2018.
6. Adams D et al. Patisiran, an RNAi therapeutic, for hereditary transthyretin amyloidosis. N Engl J Med. 2018;379:11-21.
7. Kishnani PS et al. Recombinant human acid [alpha]-glucosidase: major clinical benefits in infantile-onset Pompe disease. Neurology. 2007;68(2):99-109.