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REVIEW ARTICLE

Genetic neuromuscular disorders: living the era of a therapeutic revolution. Part 1: peripheral neuropathies

Giuseppe Vita[1,2] · Gian Luca Vita[2] · Claudia Stancanelli[2] · Luca Gentile[1] · Massimo Russo[2] · Anna Mazzeo[1]

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Abstract
Recent advances in pathophysiological and genetic mechanisms of some neuromuscular diseases and a rapid progress in new pharmacological technologies led to an accelerated development of innovative treatments, generating an unexpected therapeutic revolution. In part 1, we report already commercially available drugs, just approved drugs and new therapeutic promises in the treatment of peripheral neuropathies. Hereditary transthyretin amyloidosis (hATTR) is a devastating disease due to amyloid accumulation in peripheral nerves, heart and autonomic system. The first specific drug approved for hATTR was tafamidis, a TTR tetramer stabilizer. In 2018, the positive results of two phase 3 trials have been reported leading to start of regulatory approval route for inotersen, an antisense oligonucleotide and patisiran, the first-ever RNA interference (RNAi) therapeutic. System biology targeting approach has indicated baclofen, naltrexone and sorbitol in combination (PXT3003) as candidate drugs for Charcot–Marie–Tooth disease type 1A. This hypothesis was confirmed in experimental models and in phase 2 and 3 clinical trials. Givosiran, another RNAi therapeutic, targeting 5-aminolevulinic acid synthase, has been positively tested in acute intermittent porphyria in phase 1/2 and ongoing phase 3 trials. Although allogenic hematopoietic stem cell transplantation resulted recently a long-term therapy in mitochondrial neurogastrointestinal encephalomyopathy (MNGIE), a new strategy is liver transplantation which is able to revert the severe biochemical and clinical imbalance of the disease. Recently, a gene therapy has been tested in a MNGIE murine model, indicating that it may become a new therapeutic option.

Keywords Hereditary transthyretin amyloidosis · Inotersen · Patisiran · Charcot–Marie–Tooth disease · Acute intermittent porphyria · Mitochondrial neurogastrointestinal encephalomyopathy

Introduction

For many years, genetic neuromuscular disorders have remained without known pathogenic mechanisms and consequently with no treatment. In 1988, the complete sequence of Duchenne muscular dystrophy cDNA was determined [1] and its protein product, named dystrophin, was identified as responsible of the disease [2]. Later on, the discovery of dystrophin-associated glycoproteins linking sarcolemma and sarcoplasm to the extracellular matrix [3] opened a wide window of knowledge about pathogenesis of many other skeletal muscle disorders. In the same time, the development of new genetic technologies, advances in gene transfer and modification technologies has led to a cautious optimism, greatly enhancing the possibility of a successful therapy [4].

In 1983, the United States of America (USA) Orphan Drug Act had been established to enhance market incentives and decrease regulatory barriers for products used to treat rare ("orphan") diseases [5]. In 2000, the European Parliament approved the Orphan Medicinal Product (OMP) Regulation to develop medicines for rare diseases, designated on the basis of epidemiological data, medical plausibility and potential benefit. However, despite incentives for sponsors/pharmaceutical companies to develop OMP, a small number of products and very few innovative drugs were licensed in the first decade of OMP legislation [6], being particularly true for neuromuscular disorders.

Giuseppe Vita and Gian Luca Vita contributed equally to this work.

✉ Giuseppe Vita
vitag@unime.it

[1] Unit of Neurology and Neuromuscular Diseases, Department of Clinical and Experimental Medicine, University of Messina, Messina, Italy

[2] Nemo Sud Clinical Centre for Neuromuscular Disorders, Messina, Italy

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In the last years, advances in the understanding of pathophysiology and genetic mechanisms of some neuromuscular diseases together with a fast progress in new drug technologies led to an accelerated development of innovative therapeutic approaches, producing an unexpected revolution. Drugs identified by systems biology analysis, antisense oligonucleotides (ASOs), non-replicating adenoviral vector carrying a human gene, small molecule stabilizers of mutant protein and RNA interference (RNAi) technology have been tested in successful clinical trials. Some drugs already obtained market access and some others are close to achieve it. This two-part paper reviews recent achievements in the pathogenic mechanisms, clinical aspects and therapeutic strategies of genetic diseases of peripheral nerve (part 1) and motor neuron and skeletal muscle (part 2), including already commercially available drugs, just approved drugs and new therapeutic promises.

Hereditary transthyretin amyloidosis

Hereditary transthyretin (TTR) amyloidosis (hATTR) is a progressive devastating disease transmitted as an autosomal dominant trait, characterized by multiple organ failure including axonal sensory-motor neuropathy, cardiac involvement and autonomic dysfunction, kidney and gastrointestinal involvement and vitreous opacities. Amyloidosis occurs because of destabilized misfolded variant TTR protein generating amyloid fibrils which accumulate into body tissues [7, 8]. Suggested pathogenic mechanisms include endoneurial oedema, nerve ischemia, oxidative stress, inflammation and apoptosis [8–11]. It accounts one to three tens of thousands of cases worldwide, with Val30Met mutation identified in the majority of the patients and endemic foci in Portugal and Mediterranean area, Sweden and Japan [12]. However, more than 150 amyloidogenic TTR mutations have been recognized, with varying geographic distributions, and organ involvement [7, 13, 14]. In elderly people, deposits of TTR protein cause a condition called senile systemic amyloidosis, without any mutation in the TTR gene. For yet unknown reasons, wild-type TTR protein begins to form amyloid deposits typically in the heart, causing slowly progressive heart failure (disease named wtATTR) [15].

hATTR onset occurs between the third and eighth decades of life and patients are classified having early (before 35 years) or later (after 55 years) onset [16, 17]. Peripheral neuropathy begins with involvement of both superficial and deep sensation in the distal extremities, followed by loss of all sensory modalities and motor involvement [18]. Dysautonomia includes postural hypotension, a feeling of fullness in the stomach, nausea and vomiting, diarrhoea and/or constipation, weight loss, dysuria followed by incontinence and erectile dysfunction [19]. Cardiomegaly with thickening of the interventricular septum and granular sparkling on echocardiography and atrioventricular conduction block requiring pacemaker implantation characterize the heart involvement. Cardiac scintigraphy with technetium-labelled pyrophosphate tracers or heart magnetic resonance imaging may facilitate diagnosis [14, 20, 21]. If untreated, fatal outcome occurs within 10 years since the onset.

Phenotypic heterogeneity and atypical clinical presentations may lead to underdiagnosis and misdiagnosis. Frequent wrong diagnoses delaying start of treatment are as follows: chronic inflammatory demyelinating polyneuropathy (CIDP), lumbar canal stenosis, paraproteinemic neuropathy and diabetic neuropathy [22]. No response to immunotherapy in a patient diagnosed having CIDP must induce to re-evaluate diagnosis. Red flags may facilitate diagnosis when neuropathy is associated with the following: family history, autonomic dysfunction, cardiac involvement, gastrointestinal disturbances and unexplained weight loss [23, 24]. It is noteworthy that in the last years, there has been a considerable effort to better know disease natural history and to harmonize standards of care and most sensitive outcome measures [25–27].

Liver transplantation (LT) and combined heart-liver transplantation, introduced in the 1990s, provided a specific therapy by allowing for the suppression of the main source of mutant TTR. However, its effectiveness is higher in Val30Met versus non-Val30Met patients and is influenced by nutritional status, age, severity of neuropathy and cardiac involvement [28]. Other than producing variant TTR, explanted liver from a hATTR patient shows no abnormal functioning and can be transplanted into another patient with a liver failure (so-called domino LT), but de novo amyloidosis may develop 8–11 years later [29]. Orthostatic hypotension, cardiac failure, gastrointestinal disorders, malnutrition and neuropathic pain may advantage by symptomatic treatment. When nutritional status makes worse, parenteral nutrition may be useful in reducing postural hypotension, nausea and diarrhoea and increasing body weight and quality of life [30].

Tafamidis, inotersen and patisiran

In 2011, tafamidis meglumine (Vyndaqel, Pfizer) became the first specific drug approved by the Regulatory Agencies on the basis of an 18-month double-blind placebo-controlled study followed by an open label extension (OLE) [31, 32]. It is a small molecule which stabilizes the TTR tetramer, preventing its dissociation into amyloidogenic monomers. Tafamidis is not able to stop disease progression but slows worsening in Val30Met and non-Val30Met patients [33, 34]. Long-term effects have been also investigated up to 5.5 years, confirming sustained delay in the course of neuropathy with good preservation of nutritional status [35–37]. Recently, a placebo-controlled, phase 3 trial investigated the effects of tafamidis in patients with TTR amyloid cardiomyopathy.

Four hundred and forty-one patients were assigned in a 2:1:2 ratio to receive 80 mg of tafamidis, 20 mg of tafamidis or placebo for 30 months. Tafamidis treatment was associated with reduction in all-cause mortality and cardiovascular-related hospitalizations [38].

The results of two randomized, double-blind, controlled trials testing the therapeutic efficacy of two different chemically modified oligonucleotides to treat hATTR have been published in 2018. They represent a real revolution, showing that disease progression can be slowed, and perhaps reversed [39, 40]. Inotersen inhibits hepatic TTR production. It is a second generation 2′-O-(2-methoxyethyl) modified ASO which is complimentary to a region in the 3′ untranslated region of the human wild-type and all known amyloidogenic variant TTR mRNA. It binds to mRNA with complimentary base pairing mimicking the DNA/RNA complex. This hybridization leads to an RNase H1-mediated degradation of TTR mRNA, thus preventing TTR production (Fig. 1a) [41]. A total of 139 patients completed the trial (n. 87 on inotersen arm and n. 52 on placebo). The drug was administered subcutaneously every week. In the inotersen group, serum TTR levels were reduced by a median nadir of 79%. The primary end points, the modified NIS+7 (mNIS+7) and the Norfolk QoL-DN change from baseline, both showed statistically differences between the inotersen and placebo groups after 15 months of intervention and were independent of mutation type, disease stage and baseline cardiomyopathy status. Patients who received inotersen had an average increase in mNIS+7 from baseline of 5.8 (95% CI, 1.6 to 10) points compared to placebo with an average increase of 25.5 (95% CI, 20.2 to 30.8) points. An improvement in mNIS+7 (no increase from baseline) was seen in 36% of patients in the inotersen group and 50% had improvement in the Norfolk QoL-DN. Safety concerns of thrombocytopenia and renal dysfunction were managed with close monitoring [40].

Patisiran is the first-ever small interfering RNA (siRNA) therapeutic. It is encapsulated in a lipid nanoparticle delivered to intracellular compartments of hepatocytes. It specifically binds to the 3′ untranslated region of mutant and wild-type TTR mRNA, reducing both mutant and wild-type TTR production (Fig. 1b) [42]. In the largest phase 3 trial for hATTR, 0.3 mg per kilogram of body weight was intravenously administered over 80 min, every 3 weeks (totally 193 patients completed the study, 138 patisiran, 55 placebo). To minimize infusion-related reactions, all patients were pre-medicated with dexamethasone, an H_1 blocker, an H_2 blocker and oral paracetamol 60 min before each infusion. In the patisiran group, the reduction in serum TTR levels was sustained over a period of 18 months with a median reduction of 81% (range, −38 to 95) and was similar across age, sex or genotype. The primary end point (change from baseline mNIS+7) and secondary end points (change from baseline Norfolk QoL-DN, 10-m walk test and modified body mass index-BMI-) were met, with disease progression halted or even reversed. After 18 months, the least-squares mean (± standard error) change from baseline in mNIS+7 was −6.0 ± 1.7 in the treated group versus 28.0 ± 2.6 in placebo group (difference,

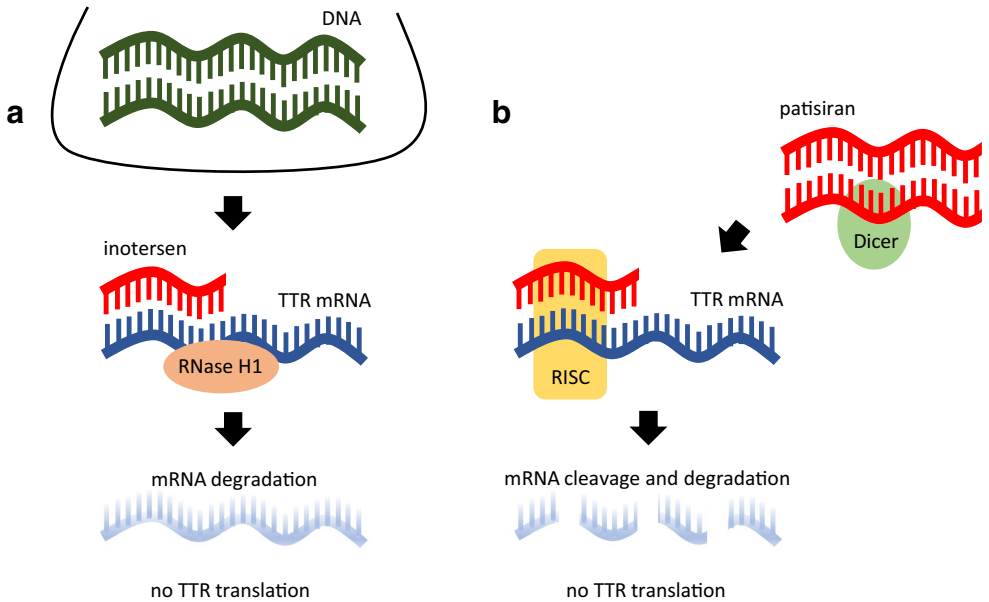

Fig. 1 Mechanism of action of inotersen and patisiran. mRNA conveys genetic information from DNA to the ribosome, where the TTR amino acid sequence is translated. Inotersen acts binding to mRNA with complimentary base pairing and leading to an RNase H1-mediated degradation of TTR mRNA and no TTR synthesis (**a**). Patisiran is a double-stranded siRNA which selectively targets TTR mRNA and triggers the RNAi pathway. The double-stranded molecule is cut into small double-stranded fragments by an enzyme called Dicer. These small fragments integrate into a multisubunit protein called the RNA-induced silencing complex (RISC), leading to mRNA degradation and suppressing its translation (**b**)

− 34 points; $p < 0.001$). Fifty-six percent of the patients receiving patisiran had an improvement (decrease from baseline at 18 months) in the mNIS+7, as compared with 4% of the patients who received placebo. Improvement relative to baseline was also seen in gait speed in the 10-m walk test (53% of the patients who received patisiran versus 13% of those who received placebo) and motor strength (40% versus 1%), as determined by the NIS weakness test at 18 months. Among all secondary end points, between-group difference in favour of patisiran was evident after only 3 months for modified BMI. The polyneuropathy disability score improved in 8% of treated patients, with transition from assisted to unassisted walking, a notable milestone for hATTR patients. Patisiran also improved hATTR cardiac manifestations, as indicated by echocardiographic measures and a reduction in NT-proBNP levels. The overall incidence and types of adverse events were similar in patisiran and placebo groups [39]. Very recently, in the absence of direct comparisons, a comparative analysis using the standard pairwise Bucher method for end points used in both patisiran and tafamidis clinical trials led to the conclusion that patisiran has a greater treatment effect that tafamidis in hATTR patients with polyneuropathy [43].

Both inotersen (Tegsedi™, Akcea Therap.) and patisiran (Onpattro™, Alnylam Pharm.) are now approved in the USA, European Union (EU) and Canada, and Expanded Access Program ("compassionate use") has been launched before starting of commercial access. Moreover, Alnylam pipeline of other investigational siRNA therapeutics includes a phase 3 study to evaluate the efficacy and safety of a new drug, vutrisiran, to be administered as a subcutaneous injection every 3 months in hATTR patients, starting early in 2019 (ClinicalTrials.gov, NCT03759379).

Charcot-Marie-tooth disease

Charcot–Marie–Tooth (CMT) disease embraces a heterogeneous group of inherited, progressive, chronic motor and sensory polyneuropathies. Patients manifest symmetric, slowly progressive distal neuropathy of the arms and legs, usually beginning in the first to third decade and resulting in muscle weakness and wasting. Typically, they show depressed/absent tendon reflexes, bilateral foot drop, painless or painful distal sensory loss and pes cavus deformity [44]. Traditional classification is based on nerve conduction velocity (NCV) parameters, which identify demyelinating (NCV < 38 m/s) (CMT1), and axonal forms, the latter with NCV within the normal (> 40–45 m/s) or in the mildly abnormal range (30–40 m/s) (CMT2) [45]. Approximately 100 disease-causing genes have been identified to date, leading to high clinical complexity and making subtype diagnosis laborious and difficult [46].

CMT estimated prevalence is about 1:2500 with type 1A (CMT1A) being the most common type accounting around 40–50% of all CMT cases. The genetic mutation responsible for CMT1A is a duplication of the PMP22 gene coding for a peripheral myelin protein. Overexpression of this gene causes degradation of the myelin sheath and nerve dysfunction. To date, no curative or symptomatic medications have been approved and treatment consists of supportive care such as orthotics, leg braces and occupational therapy or surgery. Resistance exercise as well as aerobic training may be effective in producing positive modifications in strength, daily living activities and muscle fibre size [47, 48]. Anecdotal evidence of complementary therapeutic role of sport activity in CMT has been also reported [49]. On the other hand, although the topic is controversial, overwork weakness and consequent harmful effect of exercise in CMT1A muscles seem not to occur [50], so that physical therapy should be encouraged.

Several promising compounds that modulate adenylyl cyclase activity and cAMP levels are under study in cellular and animal models, mainly targeting either the protein degradation pathway or the protein overexpression [51]. In parallel, efforts are devoted to develop sensitive-to-change outcome measures for future clinical trials [52, 53]. Transgenic mouse models and pluripotent stem cells reprogramming technology are currently investigated. Preliminary results support the use of ASOs, which are able to suppress PMP22 mRNA, as a potential treatment for CMT1A [54, 55].

Combination of baclofen, naltrexone and sorbitol (PXT3003)

Systems biology targeting approach, which is a computational and mathematical modelling of complex biological systems, was applied to CMT1A disease to obtain candidate drugs already validated in functional studies with pharmacological efficacy and safety profiles. It led to the identification of three drugs: (i) baclofen, a specific agonist of $GABA_B$ receptors which decrease the activity of adenylate cyclases and therefore reduce the levels of intracellular cAMP that positively regulate PMP22 expression [56]; (ii) the opioid receptor antagonist naltrexone hydrochloride which, at low non-toxic doses, potentiate cell signalling through opioid receptors that are coupled to inhibitory G alpha protein subunit, thereby reducing intracellular levels of cAMP [57]; and (iii) D-sorbitol, a natural metabolite playing an important role in the energy production/storage and involved in processes that are deregulated in CMT1A [58, 59]. It was hypothesized that a combination of these three drugs, named PXT3003, could decrease the toxic effects of the overexpression of PMP22 gene and also improve downstream consequences on myelination and nerve function. PXT3003 resulted to reduce levels of PMP22 mRNA in rat RT4 schwannoma cells. In vivo, its oral administration in transgenic rat model of CMT1A induced downregulation of PMP22 transcript in the sciatic nerve,

increased motor performance, restored heat sensitivity and improvement of histological and electrophysiological parameters [60].

Consequently, an exploratory, randomised, double-blind and placebo-controlled phase 2 study of PXT3003 was performed in 80 CMT1A patients with mild to moderate disability. Patients received for 1-year placebo or one of three increasing doses of drugs' combination, in four equal groups. CMT Neuropathy Score, Overall Neuropathy Limitations Scale (ONLS) and sensory conduction velocity showed a significant improvement of 8%, 12.1% and 20.1%, respectively, in the high-dose group versus the pool of all other groups. The proportion of patients who did not deteriorate after 12-month PXT3003 treatment was significantly higher in the high-dose group (79% versus approximately 48% in each of the other three groups). Non-deteriorated patients resulted those who were less affected at baseline. Safety and tolerability were good [61, 62]. On the basis of the positive results of phase 2 trial, a 15-month, double-blind, phase 3 trial was started to assess the efficacy and safety of PXT3003 in patients with mild to moderate CMT1A (NCT02579759). Three hundred and twenty-three patients were enrolled aged 16 to 65 years in 30 sites across EU, USA and Canada. For end point analysis, n. 87 was in placebo, n. 93 in lower dose and n. 55 in higher dose arms. In October 2018, the French Pharnext company announced that ONLS and 10-m walk test improved significantly in the higher dose group with no serious adverse events and therefore they intend to file for market approval in the USA and EU. In February 2019, PXT3003 received Fast Track designation by USA Food and Drug Administration (FDA). Moreover, Pharnext expects to initiate a phase 3 trial of PXT3003 in paediatric CMT1A patients in the first half of 2019 (https://www.pharnext.com/images/PDF/press_releases/2018.10.16_Ph3_Positive_Results_EN.pdf).

Acute intermittent porphyria

Acute intermittent porphyria (AIP) is the most common acute porphyria in European populations and typically the most severe. It is an autosomal dominant disorder with a much higher prevalence in Northern Sweden (23 per million) than in other European countries (5.4 per million), due to mutations in the hydroxymethylbilane synthase (HMBS) gene, markedly decreasing HMBS enzymatic activity. HMBS and other specific enzymes are responsible for hemoglobulin biosynthesis within the liver, and their deficiency in AIP and other rarer acute porphyrias leads to the accumulation of toxic intermediates, such as 5-aminolevulinic acid (ALA) and porphobilinogen (PBG) [63, 64].

AIP acute attacks occur in the age range 20–40 years, triggered by several drugs such as hormonal contraceptives, erythromycin, trimethoprim, rifampicin, phenytoin and barbiturates, by reduction in carbohydrate intake due to fasting, dieting or gastrointestinal upset, and by alcohol, infections, cigarette smoking or stress. They act by inducing the ubiquitously expressed isoform 1 of ALA synthase (ALAS1), either directly or indirectly, by increasing demand for hepatic haem. More than 400 HMBS mutations have been reported, but the estimated penetrance of acute attacks resulted ~ 1% of heterozygotes, highlighting the importance of predisposing/protective genes and environmental modifiers that precipitate/prevent the attacks [64, 65].

Recognition of an attack in a patient without a known diagnosis of acute porphyria is difficult and often delayed, as symptoms and signs are non-specific. Neurovisceral symptoms mimic a wide range of acute medical and psychiatric conditions. Abdominal pain, nausea, vomiting, constipation, high blood pressure, tachycardia, confusion and agitation up to psychosis and hallucinations occur complicated by seizures and axonal neuropathy. It is a symmetrical motor neuropathy beginning typically with proximal weakness in the upper limbs, urinary incontinence or retention, swallowing difficulties and respiratory failure [66]. Symptoms suggestive of chronic sensory neuropathy are reported by most patients [67].

Attacks are always accompanied by an increase in urinary excretion of ALA, PBG and porphyrin. Altered urine colour, darkening to red especially on exposure to light, is not specific but is well-known feature of acute porphyria, due to oxidation of PBG to uroporphyrin and porphobilin. There is usually at least a 10-fold increase of urine PBG concentration, and it may remain chronically elevated, even in the absence of ongoing symptoms [68].

Management of an acute attack includes symptomatic and supportive treatment by opiates for pain, intravenous fluids for vomiting and electrolyte imbalance. Carbohydrate loading was the standard treatment for an acute attack of porphyria prior to availability of haemin, and the rationale is based on the inhibitory effect of glucose on ALAS1. Although no effect was registered by placebo-controlled trials, haemin, which is able to suppress ALAS activity and reduce production of haem precursors, became the treatment of choice based on ability to induce faster resolution of symptoms, shorter hospital stays and a lower incidence of complications [69].

Givosiran

Preclinical studies of liver-directed siRNAs targeting ALAS1 (ALAS1-siRNAs) were performed in a mouse model of AIP. A single i.v. dose was successful in silencing ALAS1 as measured by plasma and urinary heme intermediate levels and prevented the phenobarbital-induced biochemical acute attacks for approximately 2 weeks. Injection of ALAS1-siRNA during an induced acute attack significantly decreased plasma ALA and PBG levels within 8 h, more rapidly and effectively than a single hemin infusion [70]. Successively, Alnylam Pharm.

developed a subcutaneous ALAS1 RNAi therapeutic, named givosiran. Upon administration of givosiran, the GalNAc moiety targets and binds with high affinity to asialoglycoprotein receptors expressed on hepatocytes. Once inside the cell, the RNAi therapeutic binds to and silence ALAS1 mRNA and inhibits both the translation and expression of the ALAS1 protein. This prevents ALA formation, decreases 5-ALA levels and prevents the production of PBG. In the mouse model of AIP, its single dose produced a 40% and 65% reduction of liver ALAS1 transcript, respectively, after 24 and 48 h [71].

Based on these results, a phase 1/2 randomized placebo-controlled study followed by an OLE was performed, lasting totally 22 months, using a monthly administered subcutaneous givosiran. It has demonstrated in 12 patients a mean decrease of annualized attack rates (AAR) of 93% and annualized hemin use (AHU) of 94% in givosiran-treated patients compared to pre-treatment period. Similarly, patients in the placebo arm of the phase 1 study crossing over to givosiran treatment in the OLE study ($N = 4$) experienced a mean reduction in AAR of 95% and AHU of 98%. Seven of 16 patients (44%) achieved an AAR of zero with a mean of 11.3 months on treatment; the average AAR during the run-in period for these seven patients was 15.2 (http://investors.alnylam.com/news-releases/news-release-details/alnylam-presents-updated-phase-12-open-label-extension-ole).

Givosiran has been granted breakthrough therapy designation by the USA FDA and PRIME designation by the European Medicines Agency. The safety and efficacy of givosiran are currently being investigated in the ENVISION phase 3 clinical trial (NCT03338816). It is a randomized, double-blind, placebo-controlled, multicenter study to evaluate the efficacy and safety of givosiran in patients with a documented diagnosis of an acute hepatic porphyria. Patients had been randomized on a 1:1 basis to receive 2.5 mg/kg of givosiran or placebo subcutaneously administered monthly, over a six-month treatment period. Data cut-off date of August 22, 2018 indicate 43 patients enrolled (41/43 with AIP), a $p < 0.001$ significant reduction in urinary ALA at 3 months of treatment compared to placebo, serious adverse events in 22% of patients on givosiran and 10% of patients on placebo. Topline results on completed ENVISION phase 3 study are expected in early 2019, with potential accelerated approval of regulatory agencies.

Mitochondrial neurogastrointestinal encephalomyopathy

TYMP is a nuclear DNA gene which encodes for thymidine phosphorylase (TP), the enzyme converting thymidine (dThd) and deoxyuridine (dUrd) into thymine and uracil. TYMP recessive mutations lead to imbalance of deoxyribonucleoside triphosphate (dNTP) pool, mitochondrial DNA (mtDNA) maintenance alterations with partial mtDNA depletion and multiple deletions, causing a very rare disease called mitochondrial neurogastrointestinal encephalomyopathy (MNGIE). It is characterized by severe gastrointestinal dysmotility and malnutrition, in addition to sensorimotor peripheral neuropathy, progressive external ophthalmoplegia and leukoencephalopathy, which usually lead to death in early adulthood [72]. Since dThd and dUrd accumulation is toxic, first therapeutic options were proposed to remove them from circulation through haemodialysis and peritoneal dialysis. Then, the defective TP has been replaced using encapsulate erythrocytes, isolated from patients and loaded with recombinant *Escherichia coli* TP enzyme in vitro. All these treatments correct nucleoside imbalances only with temporary improvements. The first long-term therapy was allogenic hematopoietic stem cell transplantation, which replaces TP definitively [73]. However, it is associated with difficulty finding of compatible donor and with conditioning chemotherapy, inappropriate for the severe clinical conditions of MNGIE patients. Finally, liver transplantation is a new strategy for replacing TP, because TP levels are high in healthy human liver tissues. It was successfully applied in two patients with clinical and electrophysiological improvements [74]. Recently, treatment with AAV2/8-mediated transfer of the human TYMP coding sequence targeting the liver in a murine model provided a permanent biochemical correction without adverse effects, which further indicates that gene therapy may become a practicable therapeutic option for MNGIE [75].

Conclusions

In the field of peripheral neuropathies, although there are some very interesting new candidate drugs or therapeutic procedures, RNAi therapeutics have produced so far the most remarkable results, especially in hATTR and hopefully will do in AIP. RNAi drugs are a new class of innovative medicines and a clear example of precision medicine, i.e. a treatment tailored on the basis of the ability of targeting specific mutation or mRNA and, in RNAi case, blocking protein synthesis. More than tafamidis, both patisiran and inotersen appear to be disease-modifying therapies for hATTR [39, 40, 43] and therefore raise several issues that require attention. Firstly, a population screening programme should be taken into consideration especially in endemic areas, to identify asymptomatic gene carriers of hATTR and to start early treatment [76]. Then, multidisciplinary management of hATTR patients must be improved with more extensive medical knowledge and awareness of a rare disease [26]. Patients' empowerment and their direct participation in national registries can further allow to increase adherence to standards of care and to map treatment effects in the real world and eventually post-marketing validation

[77]. Since different therapies have become available for hATTR, efforts have to be made to identify means by which to select the best therapy for single patient. A final consideration is about the cost of these new translational therapeutics reaching clinical practice. A correct cost–benefit analysis must consider long-term direct and indirect effects from the perspective of patients, their family and society.

Compliance with ethical standards

Conflict of interest G.V. discloses having been on advisory board for Alnylam Therap., Akcea Therap, and Pfizer. He is also principal investigator in clinical trials sponsored by Alnylam Therap and Ionis Therap.

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