EDITORIAL

RNA Interference and Neuromuscular Diseases: A Focus on Hereditary Transthyretin Amyloidosis

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Abstract: Neuromuscular diseases are severe disorders affecting the peripheral nervous system, usually driving to death in a limited time. Many new drugs, through RNA-interference technology, are revolutionizing the prognosis and quality of life for these patients. Nevertheless, given the increased life expectancy, some new issues and phenotypes are expected to be revealed. In the transthyretin-mediated hereditary amyloidosis (ATTR-v, "v" for "variant"), the RNA interference was demonstrated to effectively reduce the hepatic synthesis of transthyretin, with a significant increase in disease progression in terms of polyneuropathy and cardiomyopathy. The increased life expectancy could promote the involvement of organs where the extra-hepatic transthyretin is deposited, such as the brain and eye, which are probably not targeted by the available treatments. All these issues are discussed in this editorial.

Keywords: Amyloidosis, transthyretin, eye, small interference RNA, RNA interference, ocular amyloidosis.

1. INTRODUCTION

Neuromuscular diseases are intriguing as they cause severe disorders affecting the nervous system and the muscles. Some of them are considered rare diseases, and the development of effective treatment was kept aloof for many years. In the last decade, pharmaceutical engineering and the new RNA interference-based therapies, such as small interfering RNA (siRNA) and antisense oligonucleotides (ASO), gave new hope to researchers and patients. Among all, Duchenne dystrophy [1], spinal muscular atrophy (SMA) [2, 3], hereditary transthyretin-mediated amyloidosis (ATTR-v, "v" for "variant") [4, 5] and, in a short time, SOD1 amyotrophic lateral sclerosis (ALS) [6] are diseases in which RNA interference has changed life expectancy and quality of life.

Once the veil of Maya is torn, the new critical question is about the timing for starting these new treatments. "Time is muscle, time is nerve": almost all available treatments can help stop or slow down the disease progression, but the muscle or nerve lost is lost forever. In this setting, early diagnosis takes on an even greater role than in the past, and our positions about genetic tests on the asymptomatic relatives should be discussed again.

Nowadays, many genetic diseases can be diagnosed in a pre-clinical setting once a proband is identified within a family tree. Hence, the available treatments must be repeated over time, with high costs for the community. Nevertheless, a delay in treatment leads to the loss of nerve and muscle fibers. In this context, the disease onset should be well-defined to start the therapy at the right time. Despite the issue's importance, a real hallmark of disease onset is lacking for many diseases, particularly systemic ones.

A paradigmatic example is the ATTR-v. Family screening is widespread worldwide, and many asymptomatic carriers have been identified worldwide, even at a young age. In this case, the disease is characterized by a partial and poorly quantified gene penetrance, different for different mutations [7]. In the past, these questions discouraged the genetic tests in the asymptomatic family members, and a "watch and wait" approach was sometimes preferred, given the possible psychological implications of a positive gene test on people who potentially would never have developed disease symptoms. These ethical questions should be discussed again, given the changed therapeutic scenario.

A systemic involvement complicates the identification of disease onset, usually starting from the peripheral nervous system (PNS) and heart. Within the PNS involvement, large or small diameter fibers neuropathy can be the earlier onset, even within the same mutation [8]. Another possible and frequent disease onset is carpal tunnel syndrome. On the other hand, some "cardiac" mutations show the earlier involvement of the heart, which can appear as hypertrophic cardiomyopathy or a rhythm disorder. Many functional and histologic tools can be used to unveil systemic involvement [9], but a shared consensus about the definition of "disease onset" is lacking.

Another intriguing issue in therapies based on RNA-interference technology is about the target tissue. Many available therapies are focused on saving the primarily affected tissues from amyloid deposition. In the context of ATTR-v, the available

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RNA-interference therapies are approved for amyloidotic polyneuropathy, even if some evidence is developing for cardiomyopathy [10]. The PNS and heart involvement are both dependent on liver-synthesized transthyretin. Nevertheless, transthyretin is also synthesized by barrier-protected organs, such as the brain choroid plexus and the retinal pigment epithelium. The local synthesis of transthyretin in the brain and eye is responsible for the local effects of the disease, such as leptomeningeal amyloidosis and glaucoma. The effect of the available drugs on extra-hepatic synthesis has not been demonstrated yet, with some evidence showing a lower effect compared to hepatic synthesis [11]. Both the choroid plexus and the retinal pigment epithelium could share a difficulty in being targeted by RNA-interference drugs, given the barrier protection and the different receptors exposed on the cell surface. In particular, the available siRNA for ATTR-v treatment uses the LDL-receptors, and APO-E expressed on the hepatocytes to be endocytosed into the cell and explicate its effect [12]. The lack or mild expression of these receptors in the choroid plexus and retinal pigment epithelium could impair or reduce the drug's effectiveness on these specific topics. Even the other approved treatments for ATTR-v (*i.e.*, transthyretin stabilizers and liver transplantation) failed to address these items [13].

A recent phase 1 study demonstrated a reduced transthyretin synthesis in patients affected by ATTR-v and treated with the CRISPR-cas9 technology [14]. Even in this case, the LDL receptor and APO-E-mediated endocytosis were exploited to guarantee a specific action of the drug on the hepatocytes and reduce side effects. Thus, even for this therapy, positive effects on the eye and brain involvement could be ruled out.

Due to the significant impact of these drugs on the disease, a phenotype change is expected in the next years, with these probably unmet needs becoming more significant, thanks to the prolonged expected lifetime. Future prospective will certainly address these items, re-engineering the already available effective drugs to protect the barrier-protected organs from amyloid deposition.

CONFLICT OF INTEREST

Dr. Marco Ceccanti is on the Editorial Advisory Board of the journal CGT.

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