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Charcot-Marie-Tooth disease: correction of the CMT-1A phenotype

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Abstract

Charcot-Marie-Tooth (CMT) disease constitutes a group of prevalent hereditary, chronic and debilitating peripheral neuropathies. CMT type 1A (CMT-1A), the most common form of CMT, is autosomal dominant and is characterized by peripheral demyelination. No pharmacotherapies currently exist for CMT-1A, although identification of an underlying duplication in the gene for PMP22 (peripheral myelin protein 22), a glycoprotein expressed in myelin, has ignited the search for candidates to correct the CMT-1A phenotype. To date, these include the progesterone antagonist onapristone, the antioxidant ascorbic acid and the natural neurotrophic factor neurotrophin-3.

Introduction

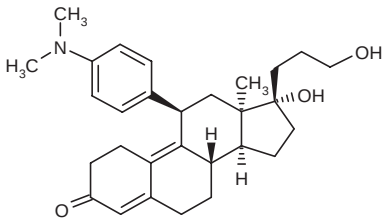
Charcot-Marie-Tooth (CMT) disease, named after the three physicians who first reported it in 1886, but also sometimes known as hereditary motor and sensory neuropathy (HMSN) or peroneal muscular atrophy, constitutes a group of genetic peripheral neuropathies that cause muscle weakness and wasting in the feet, legs, hands and forearms, as well as sensory loss in the limbs. CMT disease is estimated to affect 1 in 2,500 individuals in the U.S. alone and is the most common inherited neurological disorder. Autosomal dominant, autosomal recessive and X-linked forms have been recognized. CMT type 1A (CMT-1A), the most common form of CMT, is autosomal dominant and is characterized by peripheral demyelination and slow nerve conduction (< 38 m/s). At present, there is no pharmacotherapy for CMT-1A and current treatment options are aimed at helping patients cope with the disabling symptoms of the disease, via physical or occupational therapy, orthopedic devices and orthopedic surgery.

Targets and therapeutic advances

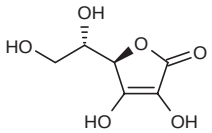
CMT-1A involves a 1.5-Mb duplication of the p11.2-p12 short-arm region of chromosome 17 (1, 2), with gene mapping indicating that the gene for PMP22 (peripheral myelin protein 22), a glycoprotein expressed in myelin, is located within this region (3). The development of animal models to mimic the CMT-1A phenotype, via *PMP22* gene overexpression and point mutations, has indicated that the severity of CMT-1A is dependent on the level of PMP22 overexpression (4). Therefore, PMP22 overexpression is an important target for novel CMT-1A treatment options, and several recent studies have identified potential candidates (outlined in Figure 1) to correct the CMT-1A phenotype.

Studies have suggested that the steroid hormone progesterone, an epigenetic regulator of gene expression, can stimulate PMP22 expression (5, 6). In accordance, daily administration of the progesterone antagonist onapristone (Schering AG) at a dose of 20 mg/kg over a period of 7 weeks has been shown to induce a 15% decrease in PMP22 mRNA in sciatic nerves in a rat model of CMT-1A. This was associated with a 1.5-fold increase in Mpz mRNA, which encodes the major structural protein of myelin. Onapristone-treated rats also maintained a significantly greater number of sciatic nerve axons and exhibited improved motor performance after 5 weeks of treatment (+65%) (7).

Further studies tested the promyelination properties of the antioxidant ascorbic acid (vitamin C) (8, 9) in CMT-1A mice. Weekly administration of ascorbic acid (1.12 mg) to male CMT-1A mice produced a significant decrease in locomotor deterioration within 1 month of treatment, with further analyses confirming an associated recovery of muscle strength (via grip tests). Treatment continuation also provided a significant improvement in mean lifespan (19.7 months *vs*. 6 months for untreated mice), which was comparable to the average lifespan of normal mice. Histological analysis of CMT-1A peripheral nerves indicated that these improvements in behavior were associated with an increased number of myelinated axons (70% on ascorbic acid *vs*. 25% on placebo) and a 10-fold lower level of PMP22 expression (10). A phase II clinical study to assess the efficacy and safety of ascorbic acid in



Onapristone, (7)



Ascorbic acid (vitamin C), (**10, 11**)

MSILFYVIFLAYLRGIQGNNMDQRSLPEDSLNSLIIKLIQADILK
NKLSKQMVDVKENYQSTLPKAEAPREPERGGPAKSAFQPVIAMDT
ELLRQQRRYNSPRVLLSDSTPLEPPPLYLMEDYVGSPVVANRTSR
RKRYAEHKSHRGEYSVCDSESLWVTDKSSAIDIRGHQVTVLGEIK
TGNSPVKQYFYETRCKEARPVKNGCRGIDDKHWNSQCKTSQTYVR
ALTSENNKLVGWRWIRIDTSCVCALSRKIGRT

Neurotrophin-3, (**12**)

Fig. 1. Therapeutic candidates for CMT-1A.

young CMT-1A patients is expected to begin shortly at the University of Amsterdam (11).

Neurotrophic agents may also be useful to promote axonal regeneration and myelination in CMT-1A. Application of neurotrophin-3 (NT-3; 5 mg/kg s.c. 3x week), a crucial Schwann cell component involved in survival and differentiation, was investigated in two CMT-1A mouse models: 1) nude mice harboring CMT-1A xenografts with characteristic delayed myelination; and 2) Trembler^{J} mice, which carry a point mutation in the *PMP22* gene and demonstrate characteristic impairment of nerve regeneration following crush injury. In both models, NT-3 significantly enhanced myelinated fiber densities, with further evidence to suggest normalization of Schwann cell-axonal interactions in CMT-1A xenografts and significantly improved Schwann cell density in the sciatic nerves of Trembler^{J} mice. Based on its *in vivo* efficacy, NT-3 was assessed in a clinical trial in CMT-1A patients. A double-blind, placebo-controlled, randomized, pilot study in 8 patients receiving human recombinant NT-3 (150 mg/kg 3x week over 24 weeks) indicated that NT-3 treatment significantly improved sensory and reflex scores, but did not affect motor scores. Examination of sural nerve biopsies from these patients indicated an associated augmentation of myelinated fiber and Schwann cell regeneration units (12).

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