Advancements in Therapy for Charcot-Marie-Tooth Disease

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INTRODUCTION

Charcot-Marie-Tooth (CMT) disease is an inherited neuromuscular disorder causing motor/sensory neuropathies and metabolic derangements. It is an important disease for primary care physicians to keep in their differentials as it is the most common genetic motor and sensory neuropathy.[1] There are multiple different types of the disease based on the genetics and the presentation. CMT type 1 results from demyelination of peripheral nerves. Type 1A is due to a mutation in the PMP22 gene. Type 1B is due to a mutation in the MPZ gene. The demyelination causes a decrease in conduction velocity resulting in weakness and numbness. CMT type 2 is due to axonal degeneration instead of demyelination. Type 2A is due to mutations in MFN2. Lastly, CMT type X and type 4 are also demyelinating neuropathies. Type X is due to mutations in the PRPS1 gene and type 4 is due to autosomal recessive mutations in SH3TC2.[2]

There are three different CMT presentations for primary care providers to be aware of. The first is a patient aged 10-30 years old with an insidious, progressive onset of bilateral leg weakness and sensory loss then eventually progresses to the hands as well. The second is in younger children with delayed walking, clumsiness, and falls. The third has a later onset in patients 40 years old with similar signs and symptoms.[1]

Currently, there are no medical treatment options for CMT. The only options are a comprehensive rehabilitation program for the weakness and possibly orthopedic surgeries or orthotics for any deformities. Exercise is another important aspect as patients should be exercising regularly in a low-intensity program.[3]

Since CMT is a genetic disease, there are many opportunities for therapy to target the gene products for the different types. In order to help physicians, I have highlighted the leading products being researched currently.

METHODS

First the CMTA website was analyzed to determine what the current areas of research are. Next, a literature review was performed using key words, such as Charcot-Marie-Tooth, genetics, and therapy, on Pubmed. Then, Charcot-Marie-Tooth was search on clinicaltrials.gov to see if there are any active trials going on and what trials have been completed. The therapies discussed were then assessed for type of CMT used to treat, if they could be used for other neurologic diseases, what stage they are currently at in testing, and what the therapy targets.

RESULTS

Eight different genetic therapies were assessed. Of these, five could be used for CMT1A, 3 for CMT1B, 2 for CMT1X, 1 for CMT4C, and 1 for CMT2. Five of the medications could be used in other neurologic diseases, including spinal muscular atrophy, amyotrophic lateral sclerosis, multiple sclerosis, facioscapulohumeral muscular dystrophy, and protein misfolding disorders. Five of the medications are still being tested in mouse models, but one of these has already been proven to be safe in humans. One medication is in phase I/IIa clinical trials, one is one phase II clinical trials, and the last one is in phase III clinical trials. Five of the therapies involve gene targeting, which including directly replacing genes, lowering mRNA expression, and altering signaling pathways. Three of the therapies involve downstream effects of the disease, including blocking axon degeneration, improving axon regeneration, and inducing muscle hypertrophy. Two additional therapies have completed supplements have completed clinical trials but have not progressed any further with treatment. Ascorbic acid was found to be effective in mouse models for CMT1A but showed no significant effects in two different phase II trials with different doses of ascorbic acid. Coenzyme Q10 completed a phase II trial for CMT2A treatment in 2013, but no results or articles have been posted. No mouse model studies have been posted either, but the supplement has been shown to be effective in Hereditary Motor Sensory Neuropathy.

Drug name/therapy concept	Types of CMT used to treat	Can it be used for other neurologic diseases?	Current stage of testing	What does the therapy target?
Schwann cell-targeted approaches: adeno-associated viral vectors[4,5]	CMT1X CMT4C	Yes (SMA)	Mouse models	Gene targeting: gene replacement
Blocked axon degeneration[6]	CMT1A CMT1B CMT2	No (no benefit in HSP)	Mouse models	Downstream effects: blocked axon degeneration
PXT3003 (baclofen, sorbitol, naltrexone)[5,7]	CMT1A	No	Phase III clinical trials	Gene targeting: lower Pmp22 mRNA expression
Antisense oligonucleotides[5,8]	CMT1A	Yes (SMA, SBMA, TTR hereditary amyloidosis)	Mouse models, but already proven safe in humans	Gene targeting
AAV1 .NT-3[5,9]	CMT1A	No	Phase I/IIa clinical trials	Downstream effects: improve regeneration capacity of distal axons
ACE-083[5,10]	CMT1A, CMTX	Yes (FHMD)	Phase II clinical trials	Downstream effects: Induces muscular hypertrophy
Gadd34 inhibition (Salubrinal)[11]	CMT1B	Yes (ALS)	Mouse Models	Gene targeting
Sephin1[5,12]	CMT1B	Yes (ALS)	Mouse models	Gene targeting

CONCLUSION

There are many different therapeutic options currently being researched for CMT. Most of these therapies are still in animal testing stages but will hopefully make progress to clinical trials soon. Most of the drugs being researched, and all the drugs currently in clinical trials are used for CMT1A. This is understandable since type 1A is the most common, and likely the first drug available will be for type 1A. There are also a wide variety of treatment types for CMT1A, so it is possible this drugs could eventually be use in conjunction with each other or for patients at different points at the disease process. In contrast, the therapies for CMT1B are mostly targeting the same aspect and hopefully one of this will prevail soon enough to progress to clinical trials. The results for the use of coenzyme Q10 will hopefully be available soon. This will hopefully lead to a new avenue of research and treatment option for CMT2A. The CMT Association website shares updates from STAR research and is a beneficial resource for clinicians to stay updated on any breakthroughs on therapy.

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