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Treatment of Charcot-Marie-Tooth neuropathies

S. Beloribi-Djefafliia PhD^a, S. Attarian MD, PhD^{a,b,c,*}

^aReference center for neuromuscular disorders and ALS, AP-HM, CHU La Timone, Marseille, France

^bFILNEMUS, European Reference Network for Rare Diseases (ERN), Marseille, France

^cMedical Genetics, Aix Marseille Université-Inserm UMR_1251, 13005 Marseille, France

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ABSTRACT

Charcot-Marie-Tooth (CMT) is a heterogeneous group of inherited neuropathies that affect the peripheral nerves and slowly cause progressive disability. Currently, there is no effective therapy. Patients' management is based on rehabilitation and occupational therapy, fatigue, and pain treatment with regular follow-up according to the severity of the disease. In the last three decades, much progress has been made to identify mutations involved in the different types of CMT, decipher the pathophysiology of the disease, and identify key genes and pathways that could be targeted to propose new therapeutic strategies. Genetic therapy is one of the fields of interest to silence genes such as *PMP22* in CMT1A or to express *GJB1* in CMT1X. Among the most promising molecules, inhibitors of the NRG-1 axis and modulators of UPR or the HDACs enzyme family could be used in different types of CMT.

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1. Introduction

Charcot-Marie-Tooth (CMT) disease is a heterogeneous group of inherited genetic neuropathies which are sensory and motor and affect the peripheral nerves. It was first described in 1886 by two French physicians, CHARCOT and MARIE, and an English physician, TOOTH.

The first signs most often appear before the age of 20 but can also occur later. The classical clinical manifestations are

a motor deficiency and distal sensory disorders, amyotrophy, and bone deformities, including the appearance of “hollow feet” [1,2]. Clinical heterogeneity is very high: associated signs are possible, their presence helps to identify the gene involved in the disease (vocal cord paresis, deafness, tremor, scoliosis, etc.), and the severity of the disease is very variable, ranging from asymptomatic forms in adults to very disabling forms in children. The worsening is progressive [3].

There are two main forms of CMT, which are essentially differentiated by their electrophysiological phenotype: the demyelinating form (type 1) and the axonal form (type 2). However, in a certain number of families, patients present characteristics that are not clearly classified as demyelinating or axonal. Thus, these families form a third group called “intermediate” CMT, representing approximately 10% of patients [4].

A nerve conduction study (NCS) helps to establish the diagnosis and is the first step in classify the neuropathy [5].

Transmission can be autosomal dominant, autosomal recessive, or X-linked. The occurrence of *de novo* mutations is frequent for the CMT1A form for all three forms [6].

Purely motor forms (known as “spinal” CMT, hereditary distal motor neuropathy, or distal spinal amyotrophy) are possible, as well as purely sensory and/or dysautonomic forms. These disorders are considered to be “CMT-related” disorders and are sometimes classified as axonal CMT (CMT2).

The diagnosis of the different subtypes is based on the identification of the causal genetic abnormality. Clinical examination, mode of transmission, and NCS characteristics enable to lead the molecular diagnosis using targeted or high-throughput sequencing and validate the results. More than 100 genes have been identified in CMT disorders, but there are four major forms associated with four different genes, which represent 90% of all CMT cases [7]:

- CMT1A, due to PMP22 duplication, is the most common CMT disorder (60.5%) with an autosomal dominant inheritance;
- CMTX1, due to GJB1 mutations, is an intermediate type (16.7%) and X-linked;
- CMT1B, due to MPZ mutations (9.4%), has an autosomal dominant inheritance;
- CMT2A, due to MFN2 mutations (4.4%), also has an autosomal dominant inheritance.

Currently, there is no curative treatment for CMT. Thus, the management of CMT involves therapy to treat the symptoms. The aim is to prevent complications using motor and proprioceptive physiotherapy, foot lift orthoses, podiatry care, and occupational therapy. Physical therapy is proposed to avoid musculoskeletal complications.

Regular practice of moderate sports activities adapted to muscular capacity develops muscular strength and endurance and reduces feelings of fatigue and pain in patients and is therefore encouraged.

Thanks to scientific progress in the last three decades, new therapeutic strategies have been developed according to the pathophysiology of the different CMT types, new molecules or combinations of molecules are studied, and drugs based on RNA, DNA, and CRISPR/Cas9 technologies are being developed. This review will describe clinical trials that are ongoing or in preparation as well as the most promising perspectives in the main and the rare CMT forms [8].

2. Management

Currently, there is no drug capable of counteracting the disease, so patients’ management is based on rehabilitation and occupational therapy with psychological support.

CMT neuropathy is a chronic condition requiring well-coordinated multidisciplinary management by the various medical, paramedical, and social workers involved (neurologists, physical and rehabilitation medicine physicians, orthopedists, podiatrists, orthopedic fitters, physiotherapists, occupational therapists, and clinical psychologists).

Rehabilitation and occupational therapy aim to maintain patients’ abilities. Physical training must be adapted to each patient and include muscle strengthening, aerobic training, and relaxation [9–11]. It has been demonstrated that mild to moderate exercises reinforce upper-lower limb proximal muscles and increase strength [12,13]. Aerobic exercises on a bicycle ergometer improved cardiorespiratory functions [14]. Indeed, a 12-week aerobic training program consisting of 36 work sessions on a bicycle ergometer significantly improved of Peak Oxygen Uptake (VO₂ peak) [15].

Proprioceptive re-education consists of having patients walk on materials of different textures and densities, unstable density, on unstable surfaces (trampolines), with their eyes open or closed, or even with glasses that block a part of the visual field. The aim is to improve the proprioceptive information previously compensated by sight [16]. A pilot study conducted with 8 patients showed that a combination of stretching, muscle strengthening, and exercises focused on coordination and balance had beneficial effects on the sleep of patients and nocturnal cramps [17]. Patients are encouraged to continue the exercises learned in rehabilitation (postures, stretching) and to maintain their walking perimeter in order to retain the benefits of the rehabilitation program in the long term [9]. Muscular work causes aches and pains, which are reduced or prevented by using a device that produces vibrations with a massaging effect [16]. A recent case report showed that massage therapy (rhythmical superficial touch, myofascial release, and petrissage techniques) could decrease lumbar and foot pain and increase the lumbar range of motion [18].

The majority of CMT patients use shoe inserts to reduce foot misalignment, pain, and callosities due to foot deformities. Some patients use ankle foot orthoses (AFOs) or orthopedic shoes to correct foot drop and ankle instability (Table 1).

A custom-made shoe can be considered in more advanced cases [19]. Adapted soles help to stabilize the rear foot and to fight against foot drop; they include a fairly rigid upper lever. A discreet elevation of the front of the shoe can help the forefoot to roll. In some cases, an external sole offset can be added to stabilize the varus, a ribbing on the upper of the shoe, or even an integrated lift. However, the latter will make the shoe heavier.

Lifter-type orthotics (over-pedic orthotics) are designed to improve balance and stability when walking and to control stepping in the oscillating phase. There are different models: standard or molded lifts. The materials used are varied: fabric with an elastic return strap, polypropylene, or carbon.

The balance and the temporospatial parameters of walking with a standard shoe alone, a standard lift (plastic AFO), and an elastic AFO were compared in 26 CMT patients by Guillebaste et al. Only the standard lift improved balance. The two types of orthoses resulted in an increase in step length. The authors identified criteria that help in prescribing

Table 1 – Comparison of AFOs and orthopedic footwear.

Type of AFO	Patients	Improvements, observations, recommendations	References
Plastic vs. Elastic AFO	26	Both types of AFO increased step length Plastic AFO improved balance	[20]
Custom made AFO: patients had to get used to their AFO during 10 weeks. Then, they were asked to walk with and without	8	Participants walked faster, with longer steps and greater frequency in the braced Improvement of dynamic functions: subjects loaded the brace tibial shell during propulsion, and that the load on the brace increased with walking velocity	[17]
Freedom, soft and ankle brace	14	Decreased the steppage and the proximal compensation	[22]
Regularly worn vs. not regularly worn	32 (11 patients in the AFO group, 21 in the no AFO group) patients from the AFO group had a higher disease severity and a lower muscle strenght	Patients who wore AFO were more affected than patients who do not Patients from the AFO group walked more slowly with a higher cost energy	[23]
Anterior elastics lift: patients were tested with and without their lift	7 CMT1A patients	Walking speed did not differ The energy cost was lower when patients wore their lift	[24]
Carbon fibers AFO (CF-AFO)	143 neuromuscular patients including 28 CMT patients	Anterior CF-AFO more appreciated: thinner, lighter, better fit, more comfortable Lack of stability Better for patients with significant foot deformities and weaker dorsiflexion and plantar flexion	[26]
Comparison OS, ventral AFO, dorsal AFO, DF stop-AFO	34 neuromuscular patients including 13 CMT patients	Walking speed was increased, biomechanic properties were improved especially with dorsal and ventral AFO	[111]
Orthopedic footwear vs. standardized footwear	15 (HSMN)	OF improved walking speed (gait speed, gait length), no significant difference in balance and stability in standing position	[29]
Insoles, orthopedic shoes foot lifts	129	CMTNS and AI can be used to predict the type of the required orthosis. CMTNS < 10: no orthosis, 10 ≤ CMTNS < 15: insoles, 15 ≤ CMTNS ≤ 20: low AFO CMTNS > 21: high AFO	[28]

AFO: Ankle Foot Orthosis; CF: Carbon Fibers; DF: Dorsiflexion; HSMN: Hereditary Sensory Motor Neuropathy; OF: Orthopedic Footwear.

the type of lift. The standard lift is more suitable in cases of severe deficit. The dynamic lifter is better if plantar flexors are ≥ 4 and toe extensors ≥ 3 on the MRC score [20].

Phillips et al. in 2011, conducted a qualitative study and interviewed orthotists and patients using AFOs. They concluded that the panel of patients reported an improvement in walking speed [21]. One study compared three different orthoses frequently prescribed in England for high steppage gait: freedom, soft ankle brace, and standard lifters in 14 patients. A significant decrease in steppage gait and proximal compensation mechanisms in the oscillatory phase (hip flexion) was observed [22]. The walking performance of 32 CMT patients was also compared; the patients were divided into a group wearing a lifter daily and a group not wearing one. The results showed that patients who regularly wore their AFOs walked more slowly with a higher energy cost than CMT patients who did not use a device. Accordingly, patients with more severe impairments (high CMT Neuropathy Score, CMTNS) have a greater need for braces [23].

Walking with and without the “anterior elastic lift” brace at slow, comfortable, and fast speeds was assessed in 7 CMT1A patients. Walking speeds did not differ with and without lifters. However, the energy cost of walking was lower at a comfortable speed for patients wearing the elastic lift [24].

Another study was conducted with 8 patients who were asked to walk with and without their custom-made AFO after 10 weeks of accommodation. The walking speed and the length of the steps were improved with AFOs; the dynamic function of the AFO was also improved as most of the patients loaded the tibial brace shell during propulsion [25]. Carbon fiber AFOs were tested in 143 patients affected by a neuromuscular disease, including 28 CMT patients. It was concluded that these AFOs were more beneficial for patients presenting with ankle dorsiflexion or plantarflexion weaknesses [26]. In an Italian study of 149 people with CMT, 129 patients (87%) required orthotics, including insoles, orthopedic shoes, and foot lift splints. The CMTNS and ambulation index were the main decision criteria for prescribers of orthopedic treatment. The ambulation index was initially developed in patients suffering from Amyotrophic Lateral Sclerosis (ALS) to assess their mobility by evaluating the time and degree of assistance required to walk 25 feet [27]. No relationship or difference was found between the orthoses and the CMT type [28]. A Dutch study compared walking and prolonged standing with commercial shoes or specific orthoses in 15 people with CMT. While these aids did not improve balance (either walking or standing), they did allow the patient to walk better and faster [29]. A minority of patients needs canes, crutches, or walkers or is wheelchair-bound.

It is important to consider not only the positive impact on walking but also the level of acceptance of the orthosis by the patient. It was shown that there was a low rate of lift use (20%) in 25 patients with severe steppage gait [30]. Furthermore, patients remain reluctant to use this device if they do not feel the need for it in their daily life or if they find it uncomfortable. Finally, wearing a lift highlights their disability and worsens their feelings [31].

In general, the objectives of rehabilitation and devices (AFOs, FOs, insoles) are to maintain the extensibility of the muscles responsible for equinus and claw toes (triceps surae, toe flexor muscles), of the plantar fascia (which is responsible for the early fixation of hollow feet), and the mobility of all the foot and ankle joints (talocrural, subtalar, medio-tarsal, tarsometatarsal, intermetatarsal, metatarsal-phalangeal and inter-phalangeal). This consists of muscular and fascia stretching and joint mobilization, performed in individual sessions for better effectiveness. These exercises are also more effective if combined with massage [10].

Optimal frequency depends on two main criteria: the disease (type, stage, progression, complications) and life constraints (schooling, age, family). To be efficient on a long-term basis, the rehabilitation program should include 2 to 3 sessions per week [9,32].

For the upper limbs, it is possible to offer custom-made posture orthoses made in occupational therapy. These are most often orthoses to fight against the retraction of the finger flexors; they are worn at rest and also help fight against pain.

It is also possible to make functional orthoses to promote thumb opposition. They are used less frequently than lower-limb devices.

It is generally admitted that the improvement of muscular strength and function follows the practice of exercise by the patients, even if there is currently a lack of information on optimal exercise modality and intensity as well as on its long-term safety [11].

Nonnekas et al. have recently proposed a step-wise clinical algorithm for treating gait impairments in people with CMT. Based on clinical observations, this algorithm leads to conservative, such as wearing AFOs, or surgical treatment [33].

3. Surgical management

Rehabilitation and orthoses can improve symptomatology [34], and consequently, those with physical therapy are preferred. Surgery can be performed for orthopedic deformities of the extremities, such as hollow feet, claw toes, claw fingers, scoliosis, or steppage gait. Different surgical techniques can be proposed; however, a single operation is usually insufficient, and multiple surgical procedures are necessary to reach the expected aim.

Data from a large international cohort showed that foot deformities were reported in 1914 of 2706 patients (71%) with CMT and related disorders, and 30% of patients required surgery to correct foot deformities [35].

Orthopedic surgery can be proposed to correct severe foot deformities and bone deformities with muscle imbalance. Surgery is indicated as the last resort when physical therapy or the use of orthoses have failed. Several surgical procedures

have been described, such as plantar fascia release, tendon transfers, and tendon lengthening; posterior tibial tendon transfer was first described in 1982 [36]. For example, the claw foot, characteristic of CMT, can be corrected with the Jones Tendon Transfer. This deformity is due to muscular imbalances concerning the long flexor, the extensor tendon and the peroneus longus. This operation requires a rigorous muscle strength evaluation of the extremities to be performed, and is generally followed by a hallux interphalangeal fusion for better results [37]. Corrective osteotomies, such as calcaneal osteotomy and first metatarsal osteotomy, may be performed when the deformity is more severe or has become rigid. To correct the pes cavus or equinovarus deformities, the tarsometatarsal resection or metatarsal osteotomy can be performed [38,39]. Although multiple calcaneal osteotomies have been described, the choice of a procedure depends of the nature of the deformity, the expectations and the preference of the surgeon. It was suggested that the subtle cavovarus should be managed with a lateral osteotomy [40]. Authors proposed in 2010 an algorithm for the surgical management of the subtle cavovarus foot. From the initial Silfverskiöld test (that differentiates gastrocnemius tightness from an Achilles tendon contracture by evaluating ankle dorsiflexion with the knee extended and then flexed) [41], they suggested which procedure should be performed according to the observations resulting from the previous surgery until the expected result [42]. Foot and ankle deformities can be corrected with the gastrocnemius lengthening notably. Postoperative risks, such as nerve injury and weaknesses are rare but have to be mentioned [43].

In general, several surgical procedures are required to correct deformities, and the decision must be adapted to each patient [44–46]. Only a few studies are focusing on these surgical operations and their long-term benefits, so there is a lack of evidence and guidelines.

It is noteworthy that approaches vary between centers in the same country and between different countries. Recently a team of experts proposed a consensus statement regarding surgical treatment of CMT and defined standardized templates for history and physical examination while recommending the involvement of surgeons earlier in disease management [47]. A recent study showed that CMT patients ($n = 63$) who had foot surgery maintained a high gait efficiency over time. The majority of patients expressed their satisfaction [48].

It was also reported that orthoses and tendon transfers improved the pinch and grasp function. In addition, Pisciotta et al. specified in 2021 that nerve release or transfer to relieve entrapment neuropathies could be performed but had to be submitted to a careful decision. Most patients recover spontaneously from palsies related to entrapment. Thus it was suggested that surgery should be reserved for patients with persistent symptoms [8].

Scoliosis occurs in 20–30% of patients. First-line treatment involves bracing, physical therapy, and rarely surgery [49,50]. Surgery, as for foot deformities, is the last resort. As there is no scoliosis specifically related to CMT, unlike muscular scoliosis, its surgery should be considered regarding the indications of idiopathic scoliosis. Surgical fusion, mostly posterior spinal fusions, is not associated with complications, but neuromonitoring remains difficult. Thus, there is still a lack of follow-up and knowledge regarding the benefits of scoliosis surgery [50].

In cases of hip dysplasia, “Bernese” periacetabular osteotomy can be used. The first results were reported by Trumble et al. in 1999 on a cohort of 115 patients, 4 of whom had CMT [51]. The latest study published in 2016 compares this treatment in 27 CMT patients and 54 patients with “developmental” hip dysplasia [52]. CMT patients reported an improvement in scapular hip pain after surgery. However, there were higher risks of complications: 33% of CMT patients versus 13% of control patients (sciatic neurapraxia, sciatic palsy, ectopic ossification, infection, pubic disunion, persistent pain, hip arthroplasty).

4. Pain and fatigue

In CMT, pain can originate from nerve damage (neuropathic pain): tingling, burning sensation, and electrical discharge. Other mechanisms can also cause pain (musculotendinous retractions, joint deformity, hyper-pressure point). An Italian study was carried out on 50 patients with CMT, including 19 CMT1A, 12 CMTX1, 11 CMT due to the MPZ gene, and 8 CMT 2A. Thirty-six percent of patients experienced pain. This was neuropathic in 15% of cases, occurred more often in the extremities, and seemed to be strongly linked to damage to A δ fibers [53].

The usual pain-killing drugs are antiepileptic drugs and antidepressants, but these treatments have not been evaluated specifically in CMT [54,55]. NSAIDs, paracetamol, SSRI drugs, and anticonvulsant drugs can be prescribed [56], but opioids are to be avoided. Some patients require pain management in a dedicated center.

CMT patients (85%) complain about muscle cramps [57], and only rehabilitation therapy and relaxation exercises have shown any efficiency in this domain [58].

Fatigue is also frequently reported by CMT patients and has a negative impact on the quality of life of patients [23,57].

On one hand, the presence of fatigue predominantly in the morning is usually functional, and even more so of excessive daytime sleepiness. Thus, it should lead to an investigation for sleep respiratory disorders. The prevalence of Obstructive Sleep Apnea (OSA) is increased in CMT1, and cases of central apnea have also been described. The restless legs syndrome, more present in CMT1 and CMT2 populations than in the general population [59], may also lead to insomnia, a reduction in total sleep time, and sleep fragmentation in the case of periodic movements, which may result in morning fatigue associated or not with excessive daytime sleepiness. On the other hand, a fragmented, non-restorative sleep should be evocative of sleep disorders. Thus, this fatigue can also prompt to search for depressive syndrome and nutritional deficiencies.

5. Therapeutic education and lifestyle adaptation

Therapeutic education is a set of activities (awareness, information, learning, psychological and social support) designed to help the patient (and his or her family) understand the disease and treatments, participate in care, take charge of his or her state of health and encourage, as far as possible, the

maintenance of daily activities. It must take into account the person as a whole by evaluating personal projects, the experience of genetic neuropathy, and the patient’s knowledge. Therapeutic education must ensure that the patient and his or her family have a good understanding of the information related to the disease and its management [60].

6. New strategies

Currently, there is no specific treatment for CMT. Many studies are currently underway, from bench research to applied strategies. Most of them focus on restoring the levels of inhibited proteins and/or decreasing the levels of mutated proteins. These strategies have to consider the balance of protein levels; for example, the duplication of PMP22 is responsible for CMT1A, whereas its down-regulation induces HNPP. Figs. 1 and 2 present the targeted pathways and genes in CMT1A and other CMT, respectively.

7. Clinical trials

7.1. CMT1A: Ascorbic Acid

Ascorbic acid, which showed encouraging results in mice models, was not beneficial to CMT1A patients. Indeed, this therapy had no significant effect in 3 randomized, double-blind, unbiased placebo vs. treated studies with a dose of 1 to 3 g/day for 12 days [61], with a dose of 1.5 g/day for 24 months [62] and with a higher dose of 4 g/day for 24 months [63].

7.2. PXT3003 (Pharnext)

CMT1A is characterized by a PMP22 mutation which leads to overexpression of the PMP22 protein. This, in turn, leads to myelination defects. PXT3003 is a mixture of low doses of baclofen, sorbitol, and naltrexone that can lower PMP22 expression through different mechanisms and is expected to act synergistically. Baclofen, a γ -aminobutyric acid (GABA)-B receptor agonist usually prescribed to relieve spasticity, acts via the cyclic adenosine monophosphate (cAMP)-dependent silencer element to negatively regulate PMP22 transcription in Schwann Cells (SCs). Naltrexone is an opioid antagonist used to treat opiate and alcohol dependence which induces endogenous endorphin release and thus increases cell surface targeting of cognate opioid receptors, able to potentiate the adenylate cyclase-inhibiting effect of endogenous opioids on the level of PMP22 expression. D-Sorbitol, a carbohydrate alcohol found in the food industry (E420) and a laxative, can bind with high affinity to muscarinic receptors involved in PMP22 expression and possibly improve protein folding. Preclinical and clinical studies showed that PXT3003 decreased PMP22 production, prevented abnormal SC differentiation, and improved neuromuscular function [64].

The ongoing international confirmatory phase III “PREMIER” trial evaluates the safety and efficacy of PXT3003 in CMT1A for 15 months against a placebo (NCT04762758). Three hundred fifty people with CMT1A have been recruited in Europe, the United States, Canada, and Israel.

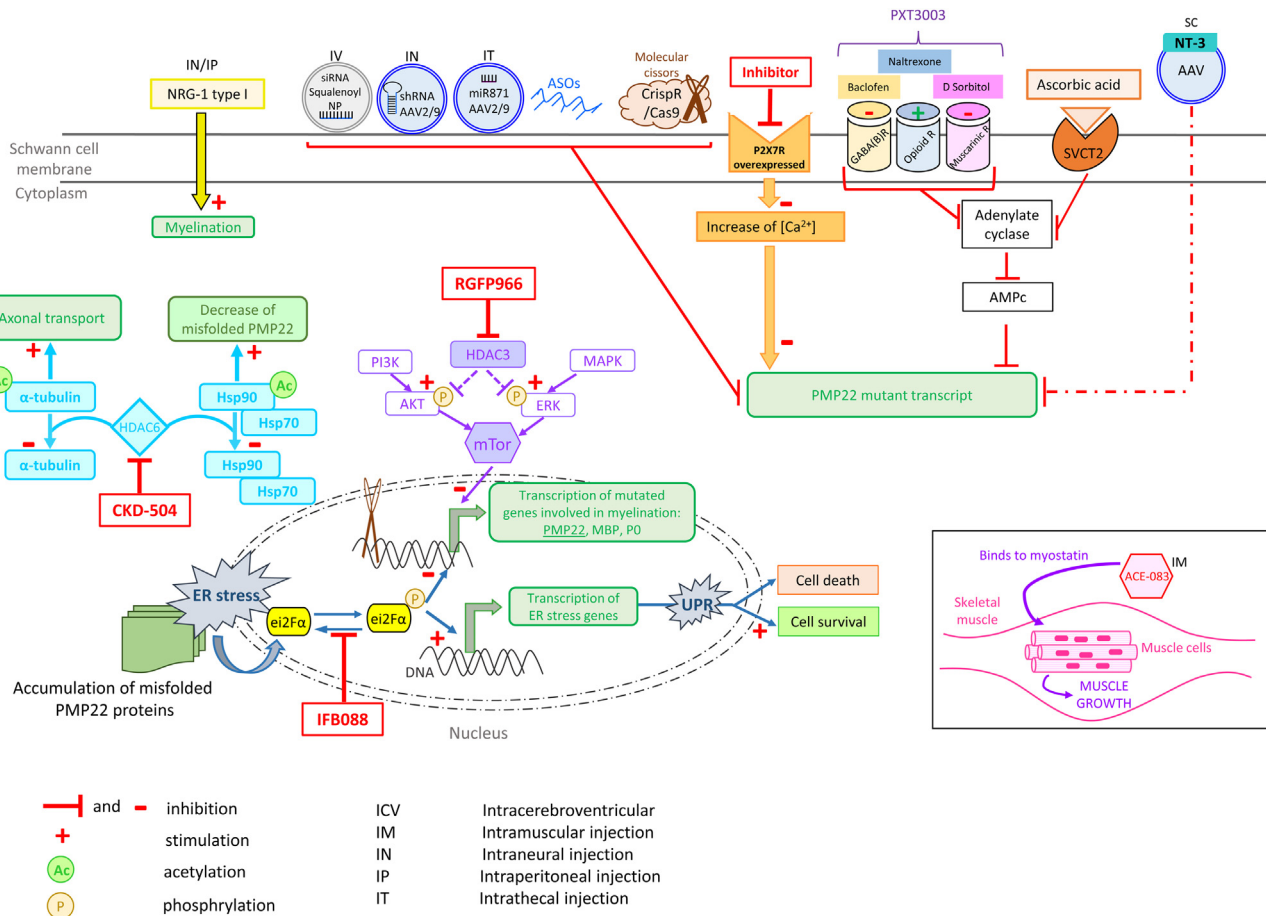


Fig. 1 – Targeting CMT1A. Schematic representation of currently tested drugs to slow down CMT1A disease progression, whether at preclinical or clinical stages. Most of them repress (directly, full line, or indirectly, dotted line) the expression of PMP22. There are different strategies. Genetic silencing and gene therapy can directly prevent the expression of the mutated protein by decreasing the PMP22 transcript. Different modes of injections are used: intraneural (IN), intrathecal (IT), and intravenous (IV). PXT3003 is the combination of three molecules that act as an antagonist (-) or agonists (+) of membrane receptors, both with ascorbic acid. They inhibit PMP22 expression through the adenylate cyclase (AC)/AMPC axis. AAV/NT-3 is subcutaneously injected to decrease PMP22 expression. Dysregulated pathways in CMT1A are represented. The activating (+) or inhibiting (-) effects of the molecules are in red. The P2X7 Receptor increases the intracellular Ca²⁺ concentration, which in turn contributes to the increase of the PMP22 transcript, which is prevented by inhibiting the receptor. The HDAC3 pathway that induces AKT and ERK phosphorylation (the mechanism is in the dotted line as it still needs to be well described) activates mTOR signaling. It promotes the transcription of mutated proteins involved in myelination. Thus, HDAC3 inhibition annihilates this transcription by preventing the phosphorylation of AKT and ERK. The HDAC6 enzyme deacetylates α-tubulin, and Hsp90/70, respectively, leading to a disrupted axonal transport and the accumulation of misfolded PMP22. The HDAC6 inhibitor reverses these processes. Accumulation of misfolded PMP22 is responsible for the Endoreticulum Stress (ER) that regulates the phosphorylation of the transcription factor ei2Fα to promote UPR (Unfolded Protein Response), which in pathogenic condition leads to cell death. Inhibition of the ei2Fα phosphorylation sustains the UPR to allow cell survival and prevent mutated gene transcription. ACE-083 binds to myostatin in skeletal muscles to enable muscle growth.

The PREMIER trial builds on the results of two previous trials:

- a French phase II trial of 80 people with CMT1A for one year [65];
- a phase III trial of 235 people with CMT1A followed for 15 months [64].

It has been shown that at high doses, PXT3003 slows or even stabilizes motor impairment. The arm and leg functions were preserved, and improved movements were reported in the high-dose group compared to the placebo group, as measured by the Overall Neuropathy Limitations Scale (ONLS). There was a significant improvement in the 10-meter timed walking test and a good treatment tolerance [64].

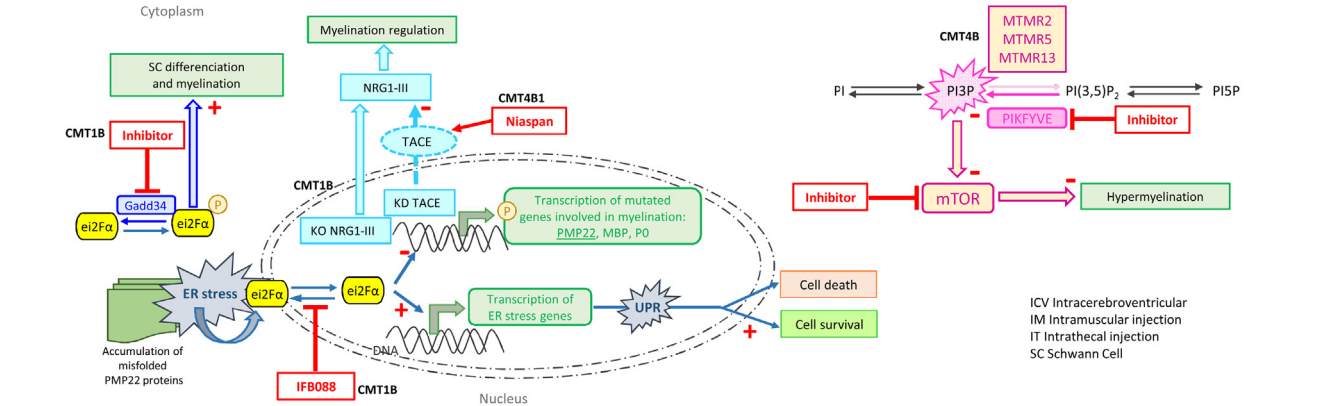
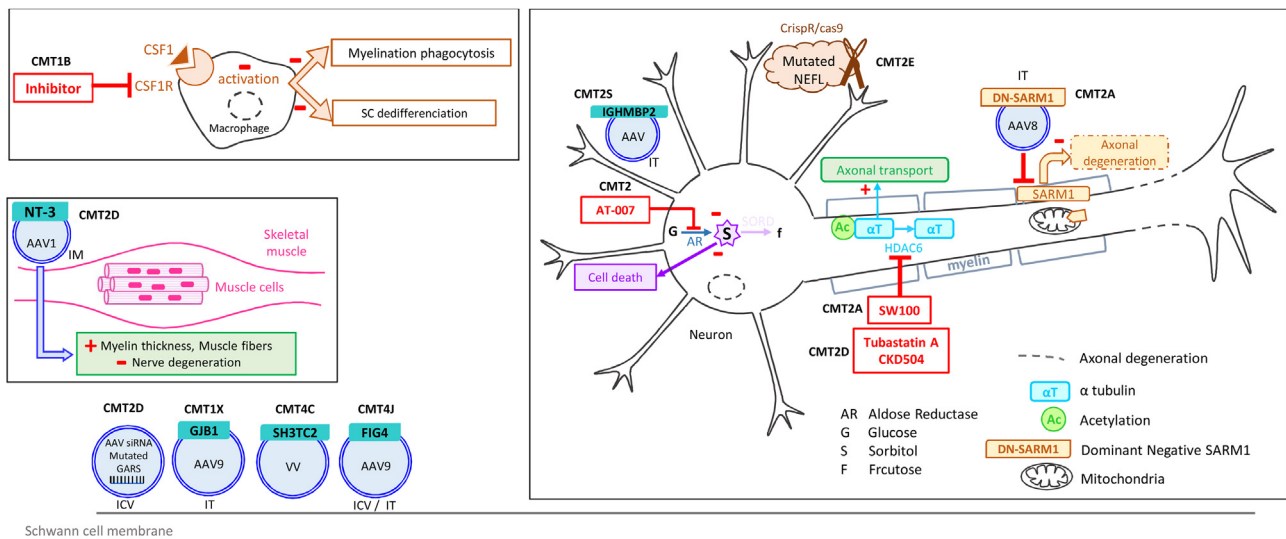


Fig. 2 – Targeting other forms of CMT. Schematic representation of targeted pathways in other types of CMT. For CMT1B, inhibiting the CSFR1R/CSF-dependent macrophage activation would prevent myelination phagocytosis and SC dedifferentiation. Targeting UPR by using IFB088 is a therapeutic perspective in CMT1B. Maintaining the ei2F α phosphorylation by inhibiting the phosphatase Gadd34 promotes SC differentiation and myelination. Knockdown (KD) of the gene that encodes the TACE enzyme or the knockout (KO) of the gene NRG1-III enables the expression of the NRG1-III that promotes myelination. Whereas in CMT4B1, the activation of the TACE enzyme by the Niaspan downregulates NRG1-III and favors myelination. In CMT4B, the inactivating mutations of the MTMR2/5 and 13 enzymes lead to an accumulation of the PI3P that promotes mTOR activity. The resulting hypermyelination can be prevented by inhibiting mTOR or the PIKfyve complex that contributes to the production of PI3P. Genetic engineering is also used to target different types of CMT by promoting or silencing gene expression through the use of viral vectors or molecular scissors at the level of muscular cells, Schwann cells, and neurons. Introducing a dominant negative of the gene SARM1 prevents axonal degeneration at the level of the neurons in CMT2 related to SORD, a toxic accumulation of sorbitol prevented by inhibiting the aldose reductase with AT-007. The inhibition of HDAC in CMT2A and CMT2D supports the acetylation of the α -tubulin and promotes axonal transport.

The PLEO-CMT expansion phase is still ongoing with 126 patients and will enable to determine the long-term effects of the drug candidate (NCT02579759).

7.3. Neurotrophin-3 (NT-3)

NT-3 is expressed by SCs to allow their survival and their differentiation along the axon. It also stimulates neurite outgrowth and myelination [66]. In preclinical models, NT-3 has been shown to improve nerve function in a xenografted model of nerve segments from CMT1A patients and in the

tremblerJ (Tr^J) mouse affected by CMT and carrying a point mutation in the PMP22 gene. Subcutaneous injections of NT-3 significantly improved axonal regeneration and enhanced myelination in both models [67]. In a pilot clinical trial, 8 CMT1A patients were subcutaneously injected with a recombinant methionyl human NT-3. The regeneration of myelinated fibers in sural nerve biopsies was improved as well as the Mayo Clinic Neuropathy Impairment Score [68]. The short serum half-life of NT-3 led to the development of Adeno-Associated Viral (AAV) vector to optimize NT-3 transfer [66]. A phase I/II clinical trial with 3 CMT1A patients aged from 18 to

35 (NCT03520751) was scheduled in 2022, as it has been delayed since 2018 because of difficulties linked to viral vector production.

7.4. ACE-083 (Acceleron)

ACE-083 acts as a follistatin that binds myostatin and other muscle regulators. Preclinical studies showed that it could increase muscle mass and strength in neuromuscular disease. No serious adverse events (AE) were observed in the phase I study [69] (NCT02257489).

Therefore, a phase II study was conducted (NCT03124459) with CMT1 or CMTX adult patients ($n = 63$). The study was divided into two parts: part 1 consisted of an open-label study to evaluate the safety and tolerability of different dose levels of ACE-083; part 2 was a randomized, placebo-controlled study, where 240 mg/muscle ACE-083 was injected bilaterally into the tibialis anterior muscle during 6 months, it was followed by a 6-months, open-label extension in which all patients received the ACE-083. Even though muscle volume and ankle dorsiflexion strength were significantly higher in patients who received the treatment vs. patients who received the placebo, clinically relevant functional improvements were not reported. As a consequence, the phase III was abandoned [70].

7.5. CMT2: AT-007 (Applied Therapeutics)

Recently, the SORD gene has been identified in CMT2. This gene encodes the sorbitol dehydrogenase enzyme. The mutation of this gene leads to the toxic accumulation of sorbitol within cells, especially nerves, which is notably responsible for neuropathy linked to diabetes [71]. Reducing sorbitol production via aldose reductase inhibition is a promising therapeutic strategy. In a pilot study with 8 patients presenting a SORD deficiency, the aldose reductase inhibitor, AT-007, was well tolerated, and the sorbitol level was significantly reduced. A phase II/III trial has recently started in Europe and the USA that targets CMT2 and dHMN (distal Hereditary Motor Neuropathy) patients suffering from a SORD deficiency (NCT05397665).

7.6. CMT2S: Gene therapy to restore IGHMBP2 gene (Alcyone Therapeutics)

CMT2S is a rare form of CMT due to mutations in the gene IGHMBP2, which encodes an immunoglobulin-binding protein 2 (IGHMBP2). Mutations of this gene are also responsible for spinal muscular atrophy with respiratory distress (SMARD1). Following promising results observed in a SMARD1 mouse model [72], an open-label study began at the end of 2021 (NCT05152823) to test a single intrathecal (IT) injection of an AAV9 vector carrying IGHMBP2. This study will recruit 10 children aged from 2 months to 14 years old.

8. Perspectives in major forms of CMT

Many preclinical studies have recently shown promising results for different CMT types. Some pathological mechanisms have been found in several CMT types, meaning some

strategies could be used to treat more than one disorder. Further investigations are ongoing to transpose the most efficient strategies to patients.

8.1. CMT1A

Genetic silencing. 1/RNA-interference (RNAi) is one of the developed strategies. The intraperitoneal delivery of small interfering RNA (siRNA) specifically targeting the mutated PMP22 gene allele in a CMT1A model improved neuropathic features [73]. Intravenous injection of a PMP22-targeting siRNA encapsulated in squalenoyl nanoparticles in a CMT1A mouse model decreased PMP22 levels and improved locomotor activity, electrophysiological parameters, myelination, and neurofilament levels [74]. However, the transient effects of these treatments led to the development of an AAV2/9 vector carrying murine *Pmp22*-targeting small hairpin RNA (shRNA) [75] that enabled a decrease of PMP22 and the myelin marker MPZ protein levels and improved myelination and motor function. The intraneural injection, successfully realized in animal models, is now under discussion for humans to limit viral transduction in off-target organs and lower immune response stimulation. Recently, a strategy based on the use of microRNA (miRNA) has been developed. Non-coding miRNAs are naturally present in eukaryotic organisms' genomes down-regulate their target expression at transcriptional and post-transcriptional levels. Artificial miRNAs have several advantages, as they can be delivered to target cells, as DNA cassettes, within viral vectors. Once they are transcribed *in vivo*, they produce long-term target gene silencing after one administration. Stavrou *et al.* designed an AAV-miR871, targeting conserved regions on the human and mouse PMP22 transcripts that was intrathecally injected into a CMT1A mouse model. AAV9-miR871 was administered at the early and late stages of the neuropathy: functional, morphological, and inflammatory abnormalities of CMT1A were durably restored after a single injection. No side effects were reported [76]. This promising strategy should be further investigated to allow human applications. Antisense Oligonucleotides (ASOs) were developed to silence the PMP22 transcript. Subcutaneous administration of PMP22-targeting ASOs in a mouse and a rat model decreased mRNA levels of PMP22 and reversed CMT1A features [77].

Gene therapy. CRISPR/Cas9. Molecular scissors can be used to modulate gene expression by deleting or inserting genes. In a rat SC line, CRISPR/Cas9 allowed the deletion of an upstream region of the PMP22 gene, which hosts an enhancer of the gene. This led to a decrease in PMP22 mRNA levels [78]. In a mouse model, the CRISPR/Cas9-mediated deletion of the TATA-box promoter of the PMP22 gene lowered PMP22 mRNA levels and improved nerve histology and function [79].

P2X7 inhibition. High levels of intracellular Ca^{2+} have been linked to the overexpression of the P2X7 purinoceptor/ion channel in CMT1A SCs. It has been reported that high intracellular Ca^{2+} led to the inhibition of SC maturation and differentiation, as well as inhibiting the expression and compaction of the myelin protein. Thus, the inhibition of P2X7 caused a decrease of intracellular Ca^{2+} and the restoration of the normal phenotype in CMT1A SCs, suggesting that drugs able to inhibit P2X7 could be beneficial to patients [80].

Histone deacetylase family proteins (HDAC). HDAC family proteins are involved in acetylation of nuclear and cytosolic proteins and modulate different cellular processes. They can notably act as epigenetic modifiers or regulate the activity of transcription factors [81].

In rodent CMT1A models, HDAC3 has been shown to negatively regulate myelination through PI3K-AKT and MAPK-ERK pathways. In a CMT1A mouse model, it was reported that the HDAC3i RGFP966 induced myelination following activation of PI3K-AKT and MAPK-ERK1/2 signaling pathways and led to the increase of the expression of constitutive proteins of myelin (MBP, P0, PMP22), axon diameter, nerve conduction velocities, and compound muscle action potentials (CMAPs) [82]. HDAC6 is known for its actions on axonal transport through the acetylation of α -tubulin and on protein folding through the acetylation of Heat shock proteins (Hsp) 90 and 70, chaperones for protein folding. CKD-504, a selective HDAC6 inhibitor currently tested on patients suffering from neurodegenerative disorders, has been shown to reduce the level of misfolded PMP22 proteins and to induce SC differentiation. Indeed, in a CMT1A mouse model, CKD-504 was reported to induce the acetylation of α -tubulin in the nerve. In addition, Hsp90 and Hsp70 were highly acetylated, and the level of PMP22 was reduced, which led to the restoration of myelination and improved the electrophysiological parameters and motor functions of CMT1A mice [83].

Neuregulin 1. Neuregulin1 (NRG1) is a growth factor secreted by SCs and involved in peripheral nerve development. NRG-1 type I treatment has been shown to stimulate myelination after nerve injury and improve motor abilities in a CMT1A rat model [84]. The knockdown of the gene encoding TACE secretase, which inhibits NRG-1 type III activity, as well as the knockout of the NRG-1 type III gene, led to the improvement of pathological features in a CMT1B model [85]. Targeting the different isoforms of NRG-1 in other CMT types are still under investigation in both hyper- and hypo-myelinating forms of CMT [8,86].

8.2. CMT1B

CSF1-CSF1R. Previous studies have documented that low-grade inflammation involving phagocytosis by macrophages contributed to the neuropathic phenotype in mouse models for CMT1A, 1B, and 1X. It was reported that the colony-stimulating factor 1 (CSF1) activated macrophages leading to myelin phagocytosis and SC dedifferentiation and thus disturbing axonal functions. The administration of a CSF1 receptor (CSF1R) inhibitor decreased the number of macrophages in mice models without any adverse side effects [87]. In addition, it improved neuropathological and clinical features in CMT1B and CMT1X mice models. Investigations are ongoing to transpose these clinical observations to the clinical stage [88]. **eIF2 α .** As previously mentioned, MPZ mutations lead to mutant MPZ accumulation, which in turn may induce ER-stress [89]. This was shown to be accompanied by the phosphorylation of the translation regulator eIF2 α (Eukaryotic initiation factor 2-phosphorylation α), which led to the inhibition of translation and prevented accumulation of MPZ mutant proteins [90]. A mouse model resistant to eIF2 α

phosphorylation in SCs presented a worse phenotype of neuropathy with increased morphological and electrophysiological features, a decrease of myelin gene expression, and delayed SC differentiation, but effects on ER-stress levels were not reported [85]. The inhibition of the phosphatase Gadd34, that dephosphorylates eIF2 α , led to the up-regulation of eIF2 α phosphorylation and improved SC differentiation and myelination [91,92]. Thus, targeting Gadd34 or eIF2 α could be beneficial to CMT1B patients.

8.3. CMT1A and CMT1 B: IFB088 (Inflectis)

The Unfolded Protein Response (UPR) is a protective cellular reaction that occurs when cells accumulate misfolded or mutated proteins in the ER. This accumulation leads to the activation of the canonical UPR pathway and subsequent proteasomal or lysosomal degradation of non-functional proteins [89]. A high level of accumulation of misfolded proteins can trigger chronic stress, which leads to cell signaling defects and death of SCs.

It has been shown that curcumin and sephin-1, an inhibitor of eIF2 α dephosphorylation, can activate the PERK-dependent UPR, which leads to the improvement of the motor and morphological abnormalities of two CMT1B models [76,77]. In CMT1A, mutant PMP22 also accumulates in the ER, which induces UPR activation [93,94]. Thus, it has been suggested that UPR modulation could be used to treat both CMT1A and CMT1B; a recent report showed that sephin-1 (IFB-088) improved motor function, neurophysiology, and myelination in CMT1A and CMT1B mice models [95]. Consequently, clinical trials using this molecule are in preparation. The first results have shown good tolerability (NCT03610334), and a phase II trial is about to begin.

8.4. CMT2A

CMT2A, the most frequent axonal form of CMT, is caused by *Mitofusin2* (MFN2) gene mutations affecting MFN2 protein, a GTPase anchored in the outer mitochondrial membrane. This leads to abnormal mitochondrial aggregation and function, as well as dysfunctional mitochondrial trafficking along the axons. Indeed, CMT2A is characterized by axonal degeneration, in which the sterile α and TIR motif containing 1 (SARM1) protein plays a role. The IT administration of an AAV8 vector expressing dominant negative SARM1 mutants in a mouse model prevented pathological axon degeneration *in vivo*. Thus, SARM1 inhibition could be a therapeutic strategy not only for CMT2A but also for other axonal and demyelinating CMT forms with secondary axonal degeneration [86,96]. CMT2A is also characterized by a decrease of large myelinated fibers, abnormal mitochondria morphology, and disturbed mitochondrial movement within the axon. The maintenance of the functions and stability of microtubules, involved in axonal transport and mitochondria movements, is notably ensured by α -tubulin acetylation, prevented by HDAC6. In a CMT2A mouse model, where α -tubulin was shown to be hypoacetylated, the use of the HDAC6 inhibitor SW100 restored α -tubulin acetylation, motor functions of the mice through the improvement of microtubule stability, and better mitochondrial trafficking [97].

8.5. CMT1X

CMT1X is caused by mutations in the *GJB1* gene leading to the loss of expression of function of the encoding gap junction protein connexin-32 (Cx32), a myelin-related protein expressed in SCs. Hexamers of Cx32 (connexon) are components of minute intracellular gap junction (GJ) channels. Little is known about their function; the main hypothesis is that they would be responsible for the flow of K^+ and signaling molecules across the myelin sheath of SCs, to ensure myelination and maintain their functional integrity [98]. IT delivery of the viral vector carrying the *GJB1* gene in 6-month-old Cx32-deficient mice resulted in Cx32 expression in peripheral nervous system tissues of CMT1X mice. Authors reported an improvement of motor function correlated with an improvement of electrophysiological and histological features [99]. To transpose these preclinical results to patients, the same group developed an AAV9 vector to deliver the *GJB1/Cx32* gene under the myelin protein zero (*Mpz*) promoter for targeted expression in SCs. In mice that received AAV9-*Mpz.GJB1*, functional properties were improved, such as grip strength and electrophysiological outcomes. Whereas post-onset treated mice did not show significant improvements, early-onset treated mice showed an increase in hind limb force, motor performance, and sciatic nerve conduction velocities, as well as improved myelination and reduced inflammation in peripheral nerve tissues. Thus, restoring Cx32 function in at least 50% of myelinating SCs could be sufficient to provide significant functional and morphological improvement in mice models and potentially in CMT1X patients [100].

9. Perspectives in rare forms of CMT

Recent progress has enabled identifying specific genes associated with rarer forms of CMT and their pathophysiology. Thus, new therapeutic strategies are studied, mostly based on gene therapy or using inhibitors.

9.1. CMT2E

CMT2E is caused by mutations in the *NEFL* gene, which encodes the neurofilament light chain (NF-L) protein, involved in the growth of axons and the maintenance of axonal diameter and function. Missense mutations throughout the *NEFL* coding sequence cause autosomal dominant CMT2E, whereas loss-of-function mutations are recessive. Since heterozygous carriers of loss-of-function mutations were normal, it was concluded that a single functional *NEFL* allele was enough to avoid the disease. The study reported that a gene-editing strategy, based on the CRISPR/Cas9 technology and specific to a mutation, reduced the expression of the mutant allele in CMT2E motor neurons and abolished disease-associated features in a human cell model of CMT [101].

9.2. CMT2D

CMT2D is due to dominant mutations in *GARS* gene, encoding glycyl-tRNA synthetase, which causes impaired

enzymatic activity and disrupts glycine loading onto tRNA-Gly. Several reports showed that the suppression of the mutant allele of *GARS* was inefficient. Therefore an allele-specific RNAi strategy using an AAV9 vector was developed to reduce the levels of mutant *GARS* transcripts in a CMT2D mouse model. An intracerebroventricular (ICV) injection at birth prevented the neuropathy, whereas an IT injection after symptom onset was less beneficial [102]. Another strategy consisted of *NT-3* gene transfer, also using an adenovirus. As mentioned above, *NT-3* is involved in SC survival and differentiation that stimulates axon regeneration and myelination. The administration of AAV1.*NT-3* to two CMT2D mice models led to significant functional and electrophysiological improvements, as shown by an increase of myelin thickness, the reinnervation of neuromuscular junctions, and an increase in muscle fiber size [103]. Recently, human induced pluripotent stem cell (hiPSC)-based models were used to generate spinal cord motor neurons. The neuropathic phenotype of these cells was reversed upon HDAC6 inhibitor treatment with tubastatin A or CKD-504 [104].

9.3. CMT4B

CMT4B is characterized by the presence of focal hypermyelination in nerve biopsies, with myelin outfoldings made up of redundant loops of myelin lamellae. There are three subtypes of CMT4B due to loss-of-function mutations in *MTMR* (myotubularin-related protein) genes, which encode phosphatidylinositol (PI) 3-phosphatases. CMT4B1 is associated with *MTMR2* gene mutations, whereas CMT4B2 is associated with mutations in the *MTMR13* gene (also named SET binding factor 2, *SBF2*) and CMT4B3 with *MTMR5/SBF1* gene mutations. Both CMT4B1 and 2 have similar clinical features, such as an early disease onset and demyelination.

MTMR are phosphatases for which PI3P (phosphatidylinositol-3-phosphate) and PI(3,5)P2 (Phosphatidylinositol 3,5-bisphosphate) are the preferential substrates. *MTMR2* is known to form heterodimers with *MTMR13* or with *MTMR5* if *MTMR13* is absent [105].

It has been shown that disruption of Ras-related GTPase Rab35, that forms a complex with *MTMR13* and *MTMR2*, leads to the hyperactivation of mTORC1 signaling through an increase of PI3P levels and leads to focal hypermyelination. In a Rab35 KO mouse model, inhibition of mTORC1 with rapamycin led to the decrease of pathogenic hypermyelination.

The PIKFYVE complex (including active PI 5-kinase PIKFYVE, lipid phosphatase FIG4, and Vac14 protein), involved in the synthesis of PI(3,5)P2, is required for myelination. The use of a PIKFYVE inhibitor also reduced hypermyelination in a cell model. Thus, mTORC1 and PIKFYVE inhibitors represent interesting options for the treatment of CMT4B patients [106]. As mentioned above, targeting *NRG1* in hypermyelinating CMT could be efficient. Niaspan, an extended-release formulation of nicotinic acid/niacin, which enhances Tace activity and downregulates *NRG1* type III, was tested on different CMT models *in vitro* and *in vivo*. Niaspan treatment has been shown to improve myelination in neuropathic models, such as CMT4B1 [107].

9.4. CMT4C

CMT4C is due to recessive mutations of the *SH3TC2* gene (frameshift and nonsense in majority), which lead to a loss of protein function. The *SH3TC2* protein is expressed in SCs and is localized in components of the endocytic pathway, including early and late endosomes. Despite a wide range of phenotypes, CMT4C patients commonly present an early disease onset, decreased thoracic motor and sensory nerve conduction, and hypomyelination [108,109]. Using a CMT4C mouse model, a gene replacement strategy has been developed to specifically deliver the wild-type gene to SCs the gene using a viral vector. The expression of human *SH3TC2* in *SH3TC2*^{-/-} mice improved significantly several pathological features, such as the rescue of functional, electrophysiological, and morphological abnormalities [109]. Further investigations are required to transpose this strategy to patients.

9.5. CMT4J

CMT4J is caused by recessive, loss-of-function mutations in the *FIG4* gene, which encodes a phosphoinositol(3,5)P2-phosphatase. There is a wide spectrum of clinical manifestations, but in general CMT4J patients present neuron loss and demyelination in the peripheral nervous system, with vacuolization resulting from endosome/lysosome trafficking defects. An AAV9-*FIG4* vector was produced to restore *FIG4* expression in a CMT4J mouse model (ICV or IT injection). Early-treated mice had a longer life span and better motor nerve conduction, and their neuropathic symptoms were reduced. As minor unexpected side effects were reported and the strategy was well-tolerated, transposition to patients is a viable option, which requires further investigations [110].

10. Conclusions

Currently, there is no effective drug, available to slow down CMT disease progression. Therapy is based on pain-killing drugs, rehabilitation, and occupational therapy, which require regularity to be beneficial in the long term. Patients need to adapt their lifestyle to their disease and schedule their physical therapy regularly which can be difficult. This can be harder for patients who suffer from pain, fatigue, and sometimes depression. These features affect the quality of life of the patients as well as their motivation to pursue their efforts. Thus, there is a demand for efficient drug therapies. Two main strategies are being investigated: 1/Classical drugs, which act on the pathophysiology and target key factors or signaling pathways; 2/Innovating therapies based on the use of small nucleotides targeting mRNA or microRNA and, most importantly, gene therapy to stimulate or to abolish the expression of the genes involved in the disease. In the most frequent form of CMT, CMT1A, previous steps in the ongoing trial have shown positive results waiting to be confirmed. Other clinical trials are either about to start or in preparation. In addition, for all the preclinical studies that have reported promising results, ways to transpose them to patients are under further investigation.

Disclosure of interest

The authors declare that they have no competing interest.

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