

Review

The Importance of Early Treatment of Inherited Neuromuscular Conditions

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Abstract. There has been tremendous progress in treatment of neuromuscular diseases over the last 20 years, which has transformed the natural history of these severely debilitating conditions. Although the factors that determine the response to therapy are many and in some instance remain to be fully elucidated, early treatment clearly has a major impact on patient outcomes across a number of inherited neuromuscular conditions. To improve patient care and outcomes, clinicians should be aware of neuromuscular conditions that require prompt treatment initiation. This review describes data that underscore the importance of early treatment of children with inherited neuromuscular conditions with an emphasis on data resulting from newborn screening efforts.

Keywords: Inherited neuromuscular conditions, children, timely treatment, early treatment, newborn screening

ABBREVIATIONS

CHOP INTEND	Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders
CMS	congenital myasthenic syndromes
DMD	Duchenne muscular dystrophy
EAP	expanded access program
ERT	enzyme replacement therapy
GAA	acid α -glucosidase
Gb3	globotriaosylceramide
HFMSE	Hammersmith Functional Motor Scale – Expanded
HINE-2	Hammersmith Infant

IOPD	Neurological Examination – Part 2
LOPD	infantile-onset Pompe disease
LysoGb3	late-onset Pompe disease
NBS	globotriaosylsphingosin
rhGAA	newborn screening
	recombinant human acid alpha-glucosidase
RULM	Revised Upper Limb Module
SMA	spinal muscular atrophy

INTRODUCTION

Until recently, there were very few therapeutic options for patients with inherited neuromuscular diseases, but over the last twenty years, discoveries related to the mechanisms underlying neuromuscular conditions have led to the development of varied

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therapeutic approaches that have drastically changed clinical practice and patient outcomes [1]. Evidence indicates that greater benefit derives when disease-modifying and symptomatic treatments are administered early in life, emphasizing the need for prompt diagnosis. These data support the importance of implementation of newborn screening (NBS) programs that allow diagnosis of various inherited diseases within the first few days of life. To improve patient care and outcomes, clinicians should be mindful of neuromuscular conditions that require urgent treatment initiation. This review aims to assist neurologists and neurogeneticists in their clinical practice by providing an overview of evidence supporting the value of early treatment of various neuromuscular conditions. Additionally, we outline validated treatments for such use in clinical practice, the optimal timeframes for treatment initiation, and address key challenges in initiating early treatment.

It should be noted that for certain neuromuscular diseases, potential therapies are currently in development or undergoing clinical trials, but they have not yet received approval for clinical use. These diseases include X-linked myotubular myopathy, centronuclear myopathy [2], nemaline myopathy [3], limb-girdle dystrophy [4, 5], thymidine kinase 2 deficiency [6] and various other neuropathies [7]. Moreover, the significance of timely treatment has not been adequately addressed for certain drugs already available in clinical practice. Furthermore, some therapeutic options are approved for use in adults but have not been studied in children. These aspects are beyond the scope of this paper.

METHODOLOGY

The two authors prepared a list of neuromuscular and neuromuscular conditions encountered in clinical practice using a strategy described in a previous review [8] and extended based on the expertise of the authors. Appendix A provides the list of terms included in our search strategy. Three different databases (Medline (Ovid, Pubmed), Scopus, and Embase) were searched for research articles, reviews, and grey literature published since 2000. Key papers describing initial clinical trials published prior to this date were included for completeness. The two authors successively and independently screened titles and abstracts for eligibility. When the abstract was considered relevant to this review, the authors reviewed the article in detail to confirm inclusion. To

be included, studies had to meet the following criteria: (1) the study was performed on human patients, (2) patients were less than 18 years old and had been diagnosed with one of the diseases included in our list, (3) a pharmacological treatment or diet was evaluated, (4) results were presented, and (5) time to treatment was clearly stated. Therapeutics that have been discontinued or withdrawn from clinical use were not considered. Publications and/or clinical trial reports that discuss therapeutics for which time to treatment was not addressed or that are used exclusively in adults were excluded. The two reviewers compared their findings and potential disagreements were resolved by consensus. Data extraction was carried out by LM and reviewed by LS.

NEUROMUSCULAR DISEASES WITH EVIDENCE SUPPORTING BENEFITS OF EARLY INTERVENTION

Conditions requiring early drug-modifying treatment

Spinal muscular atrophy

Background and therapeutics approved for treatment of spinal muscle atrophy: Spinal muscular atrophy (SMA) is a serious inherited neuromuscular condition caused by heterozygous mutations in the *SMN1* gene, which has an average incidence of 1 in 14,848 births [9]. Mutations in *SMN1* that result in loss of function of the survival motor neuron protein (SMN) cause premature motoneuron degeneration. This condition affects both the peripheral and central nervous system resulting in proximal muscle weakness, hypotonia, and muscle atrophy [10]. In the most severe form of the disease, affected children typically present soon after birth with severe motor impairment, and premature death usually occurs within their first year of life due to respiratory failure. The severity of the phenotype is mainly modulated by the number of copies of *SMN2* [11, 12], a paralogue gene that is alternatively spliced. Little functional SMN is produced from this gene, but patients with more copies of *SMN2* have better clinical outcome [13, 14].

SMA patients were historically distributed into five types depending on age at symptom onset and motor milestones acquisition [10]. Type 0 occurs before birth, is rare, and fatal within 6 months. Types 1, 2, and 3 typically manifest in infancy but, in some cases, in adolescence. Type 4 is adult-onset. Before treatments were available, SMA was either fatal or responsible for significant and progressive disability

[15–19]. With the development of disease-modifying therapies, the clinical journey of patients has been transformed, and NBS allows patients to be diagnosed prior the appearance of symptoms in many cases. Three drugs are currently approved for clinical use in SMA, nusinersen (Spinraza®) [20–32], onasemnogene abeparvovec-xioi (Zolgesma®) [33, 34], and risdiplam (Evrysdi®) [35–38] (Table 1). All have been assessed in asymptomatic patients [39–45].

Early treatment in symptomatic patients diagnosed by symptoms: Initial evidence for the benefits of early SMA treatment emerged from clinical trials and expanded access programs (EAP) in patients with SMA types 1 and 2. In patients with SMA type 1, the ENDEAR study showed that early treatment with nusinersen (within the first 13.1 weeks of disease duration) led to better outcomes, with lower ventilation needs (23% required ventilation if treated before 13.1 weeks vs. 54% if after) and improved motor development on the Hammersmith Infant Neurological Examination – Part 2 (HINE-2) scale (93% vs. 45%) compared to later treatment [32]. In the subsequent SHINE study, SMA 1 patients treated before 5.42 months achieved higher Children’s Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND) scores, with a larger proportion achieving independent sitting (60% vs. 38%), and assisted walking (10% vs. 0%) [46, 47]. Data from EAPs in Italy and Germany showed that treatment before 7 months resulted in significantly higher CHOP-INTEND scores compared to later treatment [24, 25]. The FIREFISH study demonstrated that a higher proportion of SMA 1 patients were able to sit unassisted at 8 months follow-up when treated with risdiplam before 5 month of age (75% vs. 30%) [48]. Initiation of onasemnogene abeparvovec-xioi treatment prior 3 month of age resulted in earlier achievement of a CHOP INTEND score above 40 (median 11.9 months) [33, 49] and the ability to sit [34, 49] when compared to later start in treatment. Of note, initial findings from the clinical evaluation of the oral therapy branaplam (NCT02268552) in infants with SMA 1 who have two copies of *SMN2* also indicate greater improvement in patients treated before 4 months of age compared to those treated after 4 months [50]. However, clinical development of this molecule was halted in 2021.s

In SMA type 2, a placebo-controlled study assessing nusinersen in 66 patients (aged 2 to 12 years) showed better response rates in those treated before age 6 (64% vs. 14%) and those with shorter disease

duration [51]. Similar correlations between the age at treatment initiation and the average improvement achieved on various motor scales (e.g., Hammersmith Functional Motor Scale – Expanded (HF MSE) and Revised Upper Limb Module (RULM)) was confirmed in subsequent studies with nusinersen [23] and risdiplam [52–54]. Thus, outcomes and survival are enhanced when initiated at younger age. This prompted further study assessing treatment in pre-symptomatic patients and the development and implementation of NBS programs [55–64] to accelerate diagnosis and treatment initiation.

Early treatment in pre-symptomatic patients: The rationale for initiating treatment in asymptomatic patients was supported by evidence discussed above and by findings that indicate that rapid motor neuron degeneration occurs during the first weeks of life and even during fetal development in patients with SMA [65]. Additionally, electrophysiological studies showed reduced compound muscle action potentials in otherwise asymptomatic patients, reflecting ongoing axonal loss [60]. Three main clinical trials, NURTURE, SPRINT, and Rainbowfish, focused on pre-symptomatic patients treated with nusinersen ($n=25$) [66–69], onasemnogene abeparvovec ($n=29$) [44, 70], and risdiplam ($n=7$) [71, 72], respectively, in patients with one to three copies of *SMN2*. Pre-existing symptoms were an exclusion criterion, limiting the study to strictly asymptomatic patients. These trials showed that patients with three *SMN2* copies who were treated prior to symptom onset achieved independent ambulation before the age of two. Roughly half of patients with two copies of *SMN2* achieved typical motor milestones, whereas the other half experienced mild-to-moderate motor delay indicating significant variation in treatment response [9]. Although there is no precise equivalence between *SMN2* copy number and SMA type [73], these data clearly contrast with evolution observed in SMA2 patients from the SHINE study. Long-lasting benefits of early intervention were also evident in the five-year follow-up of subjects treated through the NURTURE trial [68]. Emerging evidence indicates potential benefits on swallowing functions due to treatment prior to symptom onset [41], but the effects on neurocognitive development require further thorough assessment.

Early treatment in patients diagnosed via newborn screening: Evaluation of SMA patients identified through NBS programs revealed that a considerable

Table 1
Summary of validated disease-modifying treatments

Disease	Molecule	Category	Mechanism	Physiological effect	Route	Dosing and Frequency	Approval	Minimum age at administration across studies	Clinical trial in PSP	Real-world data in PSP
SMA	Nusinersen	ASO	Enhances <i>SMN2</i> mRNA exon 7 inclusion	Enhances production of functional SMN protein	IT	4 loading doses (2 mg, 5 mL) First 3 at 14-day intervals. 4th 30 days after the 3rd dose. Maintenance dose every 4 months.	FDA: Dec 2016 EMA: Jun 2017	Newborn	Yes	Yes
SMA	Onasemnogene abeparvovec-xioi	AAV9- based gene therapy	Delivers a copy of SMN in a scAAV9	Permits sustained expression of the SMN protein	IV	One administration of 1.1×10^{14} vg/kg	FDA: May 2019 EMA: May 2020	Full term newborn < 13.5 kg	Yes	Yes
SMA	Risdiplam	Small molecule	Promotes <i>SMN2</i> splicing	Enhances production of functional SMN protein	Oral	0.15 mg/kg to 5 mg depending on age	FDA: Aug 2020 EMA: March 2021	Newborn	Yes	Yes
İOPD LOPD	Alglucosidase alfa	ERT	Binds to mannose-6-phosphate, is internalized and transported into lysosomes where it replaces deficient GAA endogenous enzyme	Provides exogenous source of GAA to cleave glycogen	IV	20 mg/kg every 2 weeks	FDA: Aug 2006/2010 EMA: Apr 2006	Newborn	No	Yes
LOPD	Cipaglucosidase alfa + miglustat	ERT	Binds to mannose-6-phosphate, is internalized and transported into lysosomes where it replaces deficient GAA endogenous enzyme	Provides exogenous source of GAA to cleave glycogen	IV	20 mg/kg every 2 weeks 1 h after taking oral 65 mg miglustat	FDA: Under regulatory review EMA: Mar 2023	Newborn	No	No

IOPD LOPD	Avalglucosidase	ERT	Binds to mannose-6-phosphate, is internalized and transported into lysosomes where it replaces deficient GAA endogenous enzyme	Provides exogenous source of GAA to cleave glycogen		20 mg/kg eow	FDA: 2021 (LOPD only) EMA: 2022 (LOPD and IOPD)	> 6 months of age	No	No
DMD	Deflazocort	Anti-inflammatory treatment	Pleiotropic effects	NA	Oral	0.9 mg/kg/day 0.6 mg/kg/d for the first 20 days of each month	FDA: Feb 2017 EMA: Oct 1993	≥ 4 years	No	No
DMD	Prednisone/ prednisolone	Anti-inflammatory treatments	Pleiotropic effects	NA	Oral	0.75 mg/kg/day	FDA: Feb 2017 EMA: Oct 1993	≥ 2 years	No	No
DMD	Ataluren	Stop codon readthrough	Ribosome readthrough of stop codons (for non-sense mutation)	Enables translation of full-length dystrophin	Oral	10 mg/kg tid	FDA: Not approved EMA: July 2014	≥ 2 years	No	No
DMD	Eteplirsen	Exon skipping	Promotes exon 51 skipping (amenable mutations) to restore reading frame	Promotes transcription of truncated and partially functional dystrophin	IV	30 mg/kg once weekly	FDA: Sep 2016 EMA: Sep 2018	≥ 6 months	No	No
DMD	Golodirsen	Exon skipping	Promotes exon 51 skipping (amenable mutations) to restore reading frame	Promotes transcription of truncated and partially functional dystrophin	IV	30 mg/kg once weekly	FDA: Aug 2019; EMA: Dec 2019	> 6 years	No	No
DMD	Viltolarsen	Exon skipping	Promotes exon 51 skipping (amenable mutations) to restore reading frame	Promotes transcription of truncated and partially functional dystrophin	IV	40 mg/kg/week 80 mg/kg/week	FDA: Jul 2020 EMA: Not approved	≥ 4 years	No	No
DMD	Casimersen	Exon skipping	Promotes exon 45 skipping (amenable mutations) to restore reading frame	Promotes transcription of truncated and partially functional dystrophin	IV	30 mg/kg once weekly	FDA: Feb 2021 EMA: Feb 2021	> 6 years	No	No
DMD	Delandistro-gene moxeparvo-vec- rokl	AAV9-based gene therapy	Delivers a gene encoding a shortened 138-kDA micro-dystrophin protein to muscles	Reestablishes truncated dystrophin expression to attenuate the phenotype	IV		FDA: Jun 2023 EMA: Not approved	4-5 years	No	No

(Continued)

Table 1
(Continued)

Disease	Molecule	Category	Mechanism	Physiological effect	Route	Dosing and Frequency	Approval	Minimum age at administration across studies	Clinical trial in PSP	Real-world data in PSP
Fabry	Agalsidase beta	ERT	Replaces deficient α -GAL endogenous enzyme	Decreases accumulation of Gb3	IV	1 mg/kg eow	FDA: 2001 EMA: 2003	≥ 2 years (USA) ≥ 8 years in other countries (other countries)	No	No
Fabry	Agalsidase alfa	ERT	Replaces deficient α -GAL endogenous enzyme	Decreases accumulation of Gb3	IV	0.2 mg/kg eow	FDA: Not approved EMA: Aug 2001	≥ 7 years	No	No
Fabry	Migalastat	Chaperone therapy	Increases α -GAL enzyme availability inside lysosomes by correcting the misfolding of α -GAL (for amenable mutations)	Increases α -GAL activity, decreases accumulation of Gb3	Oral	123 mg eod	FDA: August 2018 EMA: May 2016	≥ 12 years	No	No

Abbreviations: AAV9-GT, AAV9-based gene therapy; ASO, antisense oligonucleotide; CT, clinical trial; DMD, Duchenne muscular dystrophy; eow, every other week; eod, every other day; ERT, enzyme replacement therapy; IOPD, infantile-onset Pompe disease; IT, intrathecal; IV, intravenous; LOPD, late-onset Pompe disease; NA, not applicable; NS, not specified; PSP, pre-symptomatic patients; scAAV9, self-complementary adeno-associated viral serotype 9; SMA, spinal muscular atrophy; tid, three times a day; vg, vector genome.

proportion of patients have symptoms at diagnosis [56, 74], indicating that not all patients identified through NBS can be classified as pre-symptomatic. Since 2021, evidence from real-world screening programs has increasingly demonstrated benefits of early treatment [59, 62, 63, 75–85]. A recent systematic review focused on outcomes in SMA patients who have two or three copies of *SMN2* identified via NBS provides a summary of prognosis of these patients and provides an overview of the global population not restricted to pre-symptomatic patients [9]. The authors identified 77 patients with two *SMN2* copies; of these, 73 were treated at a median age of 23 days. Of the 41 identified patients with three copies of *SMN2*, 38 were treated at a median age of 52 days. Also identified were 24 subjects with four copies of *SMN2*; of these, 18 were treated at a median age of 2019 days. Of the patients with two copies of *SMN2* copies, 37% had symptoms prior to treatment, whereas 1% of those with three *SMN2* copies and 6% of those with four *SMN2* copies had symptoms. The authors concluded that patients with three *SMN2* copies and no symptoms at treatment initiation had excellent functional prognosis, achieving normal development in over 90% of cases. Patients with two *SMN2* copies had more variable outcomes [9], although their outcomes were significantly better than those identified by symptoms [83]. Due to the very small sample size, clear conclusions could not be drawn for patients with four copies of *SMN2*. The most recent recommendations, published in 2021, suggest that treatment should be initiated early for patients with four copies of *SMN2*, although there is still limited data available to support this approach [86].

Pompe disease

Background and approved therapeutics for Pompe disease: Pompe disease is an autosomal-recessive neuromuscular condition caused by mutations in the gene that encodes acid α -glucosidase (GAA). The enzyme is normally responsible for breaking down lysosomal glycogen. In Pompe disease, deficiency of GAA [87, 88] leads to glycogen accumulation, cellular dysfunction and progressive damage of smooth, cardiac and skeletal muscles [89]. As in SMA, symptom onset spans from early childhood to adulthood. Those with infantile-onset Pompe disease (IOPD) are characterized by a severe or complete GAA deficiency (<1% residual activity) [87]. Late-onset Pompe disease (LOPD) [90] is associated with a par-

tial GAA deficiency (<30% residual activity) [91] and is usually more insidious [92–95]. In patients with IOPD, symptoms may manifest within the first days of life up to 12 months of age and can occasionally be noted *in utero* [96]. Affected children experience significant motor delay and die of cardiorespiratory failure within the first year of life [94, 97].

Treatments available to date (Table 1) include enzyme replacement therapy (ERT) using recombinant human GAA (rhGAA). ERT reverses cardiomyopathy, improves motor development, and enhances overall survival [98–100]. Alglucosidase alfa (Myozyme[®]) has been used the longest and has mainly been studied in patients with IOPD. Although IOPD patients can show great improvement when treated with ERT, they often plateau and clinical decline may be observed around 20–24 months of treatment duration. Moreover, residual long-term sequelae have been observed in surviving patients, especially in those with IOPD who do not have cross-reactive immunological material (CRIM) [101–106].

A more recent version of rhGAA, avalglucosidase alfa (Nexviazyme[®]), was specifically engineered to increase glycogen clearance [107]. Ciplaglucosidase alfa (Pombiliti[®]) is another ERT, used in combination with miglustat [108]. Avalglucosidase alfa was shown to be a safe and efficient alternative to alglucosidase alfa in LOPD [109–111] and has received marketing authorization in several countries for LOPD and/or IOPD, whereas ciplaglucosidase alfa has received recent approval for adult LOPD [145]. Results from the mini-COMET trial suggest that avalglucosidase alfa is beneficial in IOPD patients who are less than 18 years of age who were declining on alglucosidase alfa [112], but the timing of treatment was not specifically evaluated. Currently, there are two ongoing open-label phase III trials assessing the safety and efficacy of ciplaglucosidase alfa in pediatric patients (<18 years old) with IOPD (NCT04808505) and LOPD (NCT03911505). Overall, data on IOPD patients treated with ERTs other than alglucosidase alfa remain very limited, and the impact of age at treatment has not yet been addressed. Several factors have shown to impact patient outcome and response to treatment including CRIM status [94, 97, 101, 113–118], the development of anti-rhGAA immunoglobulin G (IgG) antibodies [119], ERT dosage and dosing regimen [99, 100, 106, 120–122], the severity of muscle involvement at treatment onset [123], and failure to thrive at baseline [123]. Age at treatment has also been shown influence response as summarized below.

Early treatment in infantile-onset Pompe disease: The use of the terms “pre-symptomatic” or “asymptomatic” in published works can be ambiguous in distinguishing between LOPD patients without symptoms at diagnosis and IOPD patients identified through NBS who may have mild symptoms (Table 2). Clinical manifestations like increased left ventricular mass index and/or Glc4 levels have been described in most IOPD cases [124, 125], which has contributed to the ambiguity of these terms. To avoid misunderstandings across articles, it is important to provide a clear definition of these terms, similar to what has been done in SMA. As we move forward, we will discuss IOPD as a whole, using the term pre-symptomatic specifically for LOPD patients who have no clinical or sub-clinical symptoms at screening.

Alglucosidase alfa, the FDA-approved rhGAA form, was initially shown to be safe and efficient in four patients with IOPD at starting doses of 15 mg/kg or 20 mg/kg and later increased at 40 mg/kg [98]. The two patients treated before 3 months of age were ventilation-free after 36 weeks of treatment, whereas the two patients who began treatment at the ages of 7 and 8 months required ventilator support [98]. The two younger patients had no significant respiratory problems during the first 2 years of life and showed greater motor progress than the older subjects [99]. A phase I/II clinical trial confirmed cardiac and skeletal muscle function improvement in three patients with IOPD who began treatment at dose 5 mg/kg at 2.5, 4, and 4 months of age. The youngest patient exhibited significant clinical improvement, achieving normal clinical status by 16 months of age. The two other patients developed high anti-rhGAA antibody titers, declined in motor development and pulmonary function, and required ventilator support [115].

Early initiation of ERT yielded to sustained motor and cardiac improvement at 48 weeks of treatment and beyond in two patients treated at age 3.1 and 5.9 months [126, 127]. An open-label study in eight patients with IOPD treated between 2.7 and 14.6 months of age demonstrated enhanced ventilator-free and prolonged overall survival compared to historical cohort of untreated patients. Patients who received treatment before reaching six months of age had better motor outcomes and prolonged survival [128, 129], suggesting that earlier intervention yields greater advantages. Even greater motor advancements were subsequently observed after 52 weeks of treatment in a cohort of 18 patients with IOPD

who received treatment before the age of 6 months [100]. A follow-up study of 16 of these patients who had been treated for up to 3 years with ERT showed extended survival, improved ventilation-free survival, and improved cardiomyopathy compared to untreated patients [130]. Another study of 15 patients with IOPD who were treated at a median age of 13 months (3–43 months) demonstrated similar benefits [131]. Patients treated after 12 months of age had higher survival rates (90.9%) than those treated earlier (50.1%), but this reflected the high risk of death in the first year of life for patients with IOPD [131]. In addition to these studies, the value of early treatment on cardiac, biological (e.g., CK levels) and motor outcomes was further supported by case reports and small case series [125, 132]. Additionally, the correlation found between cognitive and motor development in an IOPD cohort treated before 6 months of age suggests early treatment’s impact on neurocognitive development [133].

Data from NBS programs collected since 2005 further supports the value of early intervention in infants with IOPD [134]. Most patients identified by NBS were treated within the first month of life [135–142]. Improved long-term prognosis was observed in Taiwanese CRIM-positive IOPD patients diagnosed via NBS and treated within 34 days of life, with enhanced survival and independence in ambulation after 2 years of treatment compared to natural history [102]. Patients identified through NBS who began ERT at a very young age (mean age 11.92 days; range 6–23) had superior biological, physical, and developmental outcomes and lower levels of anti-rhGAA antibodies after 2 years of treatment in comparison to a group that started ERT only 10 days later [143, 144]. Of the Taiwanese CRIM-positive IOPD cohort, 26 patients were followed for an average of 6.18 ± 3.14 years. All patients included in the study had normal heart sizes, achieved typical motor milestones, demonstrated intact cognitive function, and displayed pulmonary function that ranged from near-normal to normal [145]. Long-term study in one of the largest cohort of IOPD in France recently showed fewer benefits of ERT, with only temporary improvements followed by muscle and respiratory function deterioration; however, the impact of the age of ERT initiation was not explicitly assessed [146].

Real-world data in patients who were either pre-symptomatic or lacked clinical or chemical signs of deterioration demonstrate the benefit of higher doses of ERT (e.g., 40 mg/kg every other week and

Table 2
Publications reporting data from real-world NBS identification and treatment of IOPD

Country	Publication date	Population	IOPD (n)	CRIM +	CRIM –	Treated IOPD (n)	Pre- or asymptomatic ¹ (n)	Pre-ERT cardiac abnormalities ²	Pre-ERT laboratory abnormalities ²	Median age at diagnosis/referral*	Median age at treatment (range)	Outcomes reported	Follow-up duration (range)
Taiwan	Feb 2016	669,797	14	14	0	14	0	Y (13/14)	Y (NS)	3.02 ± 0.38*	11.92 days (6–23 days)	Yes	NS (6-year-long study)
Taiwan	Apr 2015	470,000	10	10	0	10	10	Y (10/10)(*)	Y (NS)	9 (0–33 days)	16 days (6–34 days)	Yes	6.18 years (±3.14)
Italy	Dec 2022	206,741	3	1	2	3	1/3	Y (3/3)	Y (3/3)	(3–14 day)	(5–19 days)	Yes	(1.5 –3.5 years)
Italy	Nov 2017	44,411	2	NS	NS	2	0	Y (2/2)	Y (2/2)	NA	Promptly	No	NA
Japan	Jun 2022	296,759	1	1	NS	1	0	Y 1/1	Y (1/1)	NS	58 days	Yes	14 months
USA (California)	Feb 2020	453,152	2	NS	NS	2	2*	Y (2/2)	Y (2/2)	NS	2 months, NA	No	NA
USA (Missouri)	Feb 2020	467,000	10	9	1	10	0	Y (7/8)	Y (10/10)	NS	4 days–month	Yes	NS
USA (Illinois)	Dec 2019	684,290	3	3	0	3	0	Y (3/3)	Y (3/3)	NS	10 days–6 weeks	Yes	(Several months to 4 years)
USA (Pennsylvania)	Dec 2019	531,139	2	2	0	1	1	Y (2/2)	Y (2/2)	19 days NS	21 days 10 days	Yes	31 months 6 months
Austria	Nov 2011	34,736	1	NS	NS	NS	0	NS	NS	NS	NS	No	NS

¹As labeled by authors. ²When available, the number of patients with abnormalities is shown in brackets relative to those tested. Abbreviations: IOPD, infantile-onset Pompe disease; NA, not applicable; NS, not specified; Y: yes.

20 mg/kg weekly) early in life [147, 148]. Early initiation of higher-dose ERT led to a delay in motor decline, whereas motor decline was significantly higher in patients with late ERT initiation ($p=0.006$) or late increase in ERT dosage ($p=0.044$) [147]. Of five patients who received 40 mg/kg every other week, the four who were walkers at analysis began treatment at 5, 6, 13, and 33 days of life; the non-sitter was first treated at 3.3 months of age [147].

To date, evidence supporting the benefits of early intervention in CRIM-negative IOPD patients remains limited [98, 100, 149]. A retrospective study gathered data from 20 CRIM-negative patients treated with ERT and immune tolerance induction at median ages of 2.1 weeks (0.3–3.4 weeks), 7.6 weeks (4.4–13.3 weeks), or 17.9 weeks (15.4–28.3 weeks) [149]. Clinical outcomes including invasive ventilation-free survival, left ventricular mass index, and motor and feeding status tended to be significantly better in the group treated at a median age of 2.1 weeks [149], whereas CRIM-negative patients from an historical cohort treated at median age of 13 weeks were all deceased or invasive ventilator-dependent by 27.1 months of age [114]. Due to the small number of patients, more research is needed to establish a clear understanding of the advantages in this population.

It should be noted that treatment outcomes in IOPD can be influenced by multiple factors that contribute to the complexity of comparing outcomes across studies and even within the same study. These factors will need to be carefully considered in order to understand the variations in treatment response among IOPD patients. In summary, collective evidence from clinical trial cohort studies, case series, and expert consensus [150, 151] supports the early management of IOPD patients with immunomodulation and a low-dose ERT (20 mg/kg/EOW). Additionally, the potential benefits of earlier and higher regimens have been suggested and require further investigation.

Early treatment in symptomatic and asymptomatic late-onset Pompe disease: Differentiating between IOPD and LOPD in NBS is challenging due to the limitations of enzyme assays. About 75% of Pompe disease cases are LOPD [152], and to date, there is not clear consensus regarding therapeutic strategies for treatment of pre-symptomatic LOPD and guidelines addressing this topic are sparse [153, 154]. However, evidence suggests that initiating ERT prior to the occurrence of irreversible muscle damage could yield to improved treatment outcomes [124, 155–157]. Expert consensus is that ERT should be initiated

upon the earliest onset of objective signs of Pompe disease, with pre-symptomatic LOPD patients being monitored every 6 months [158–160].

Duchenne muscular dystrophy

Background and approved therapeutics in Duchenne muscular dystrophy: Duchenne muscular dystrophy (DMD) is a progressive X-linked recessive disorder resulting from out-of-frame mutations in the gene that encodes dystrophin. Dystrophin deficiency or absence leads to progressive muscle weakness, loss of independent ambulation, and serious multisystem complications, including cardiomyopathy and respiratory muscle dysfunction, that culminates in premature death. With the advancement in multidisciplinary management and glucocorticoid therapy, patients can now live into their thirties. Although standard of care has improved life expectancy, glucocorticoids (prednisolone and deflazacort) remain the only clinically proven treatments that slow disease progression [161–163]. A variety of therapeutic strategies are being explored, and six compounds (i.e., ataluren (Translarna[®]), eteplirsen (Exondys 51[®]), golodirsen (Vyondys 53[®]), viltolarsen (Viltepso[®]), casimersen (Amondys 45[®]), and delandistrogene moxeparovec-rokl (Elevidys[®]) have received conditional regulatory approval in some jurisdictions [161, 164, 165] (Table 1).

Early treatment in Duchenne muscular dystrophy: In 2022, a systematic review explored the importance of timing of clinical interventions in DMD [166]. Of the 12 studies the authors included, six examined glucocorticoid timing [167–172] and one focused on ataluren [173]. There is low-quality evidence that earlier initiation of glucocorticoids prolongs ambulation in patients with DMD, but these agents may also decrease cardiac and respiratory health. The evidence suggesting that early initiation of ataluren improves lower extremity and motor function was graded as being of very low quality. Given the limitations of the studies reviewed, such as confounding by indication, small sample size, and lack of longitudinal follow-up, the authors concluded that the optimal timing of clinical interventions, including glucocorticoids and ataluren, in DMD is still unknown and that further research is needed [166]. Expert recommendations slightly differ, yet generally lean toward advocating steroid trials for children aged 2 to 5 [174–177]. Notably, in June this year, delandistrogene moxeparovec-rokl (SRP-9001) gained FDA approval to treat ambulatory pediatric patients aged

4 to 5 with certain DMD gene mutations. Approval was based on a double-blind placebo controlled phase 2 trial, including 43 patients, of whom 41 subjects received study treatment (20 subjects in the SRP-9001 group and 21 subjects in the placebo group) [164].

Fabry disease

Background and approved therapeutics in Fabry disease: Fabry disease is a life-limiting X-linked inherited lysosomal disorder caused by pathogenic *GLA* variants [178–180]. These mutations result in inadequate activity of α -galactosidase A, leading to the accumulation globotriaosylceramide (Gb3), and its deacylated form, globotriaosylsphingosine (lysoGb3) within lysosomes in various tissues. As in Pompe disease, accumulation of metabolites causes cellular damage and dysfunction and structural damage to organs [181–184]. Clinical manifestations are numerous and include small fiber neuropathy, renal failure, cutaneous rash, neuropathy, stroke, and cardiomyopathy [180].

GLA variants associated with minimal or no α -galactosidase A activity occur in males and lead to the classic Fabry phenotype with early onset of symptoms and progressive multisystemic involvement. Patients experience acroparesthesia during childhood, but renal, cardiac, and cerebral involvement is typically not detectable at that stage [185, 186]. Cardiac left ventricular mass increases and albuminuria develop during adolescence. Subsequently, ECG changes, cerebral white matter lesions, stroke, and myocardial and glomerular sclerosis ensue, resulting in cardiac complications, renal failure, severe morbidity, and death by the age of 60 [187, 188]. In classic Fabry disease, the variant Gb3 is thought to accumulate *in utero* [189, 190] so that organ damage manifests early in life [191, 192]. In females, the clinical severity of Fabry disease varies considerably [193, 194] due to the presence of residual α -galactosidase A activity and X-chromosome inactivation patterns [179, 195, 196]. Although symptoms in woman often manifest during childhood, they usually appear at later stages than in males [197, 198].

Agalsidase beta and agalsidase alfa are the two ERTs approved for treatment of Fabry disease that have been available since 2001 [199–201] (Table 1). Both drugs are approved in adults and adolescents; agalsidase beta is approved for use in children aged 8 years and above, and agalsidase alfa is approved for use in children aged 7 years and above. Migalastat, a pharmacologic chaperone, is another oral treatment

approved for Fabry disease patients aged 12 years and above with amenable *GLA* variants (Table 1). Migalastat stabilizes renal function and reduces cardiac mass [202, 203], offering an alternative to ERT in adult patients [204]. Data regarding the impact of treatment timing are not available at the time of this review.

Early treatment with enzyme replacement therapy in Fabry disease: The safety and effectiveness of managing Fabry disease with both agalsidase alfa and agalsidase beta were demonstrated in pivotal trials and related open-label extension studies. Agalsidase alfa and beta initially induce a clear biochemical response in adults, reducing Gb3 levels in plasma and urine [200, 201, 205, 206] and clearing storage material from endothelial cells and various renal cell types [207]. From a clinical perspective, although the response was highly variable, ERT improved neuropathic pain [201, 208], renal function [201, 209], cardiac function [201, 210–213], gastrointestinal symptoms [214, 215], and quality of life [216]. These benefits were confirmed by real-world data and follow-up studies [217–220], some of which also demonstrated a delay of clinical events in treated patients [214, 218].

Agalsidase beta (1 mg/kg) was well tolerated and efficacious in a 48-week open-label study of patients aged 8 to 16 years [199]. The treatment resulted in clearance of Gb3 from dermal capillary endothelial cells and reduction in gastrointestinal symptoms [199]. Agalsidase alfa also had good safety and tolerability profiles in pediatric populations [221, 222]. An open-label follow-up study in young patients (age range: 8.6 to 17.3 years; 90.9% males) treated with agalsidase alfa for 6.5 years showed that the ERT was tolerated long term and that reductions in plasma and urinary Gb3 levels were maintained, that left ventricular mass and eGFR were normal, and that heart rate variations were reduced [223].

Multiple prospective, follow-up, and retrospective studies mostly in adults have indicated that initiating treatment at an early stage of disease prior to irreversible organ damage leads to improved clinical and biological outcomes [224–230]. Despite the encouraging evidence supporting early treatment, the optimal timing for initiating treatment remains uncertain. In a study of 12 patients with classical Fabry disease, the greatest clearance of podocyte Gb3 inclusions at 65 weeks of treatment was observed in the youngest patient, aged 7 years old [231]. In a retrospective cohort study, initiation of ERT at less than

25 years of age in men with classical Fabry disease led to a better biochemical response, with higher odds of achieving a plasma lysoGb3 levels below 20 nmol/L and significantly lower lysoGb3 levels one year after ERT initiation compared to those who started treatment later in life [232]. In a retrospective study of seven males with classical Fabry disease who received agalsidase beta treatment during childhood [213], evaluation after 10 years (median age 24 years, range 14–26) showed reduced albuminuria, lower left ventricular mass, absence of myocardial fibrosis, and normal eGFR compared to untreated patients [217]. The authors suggested that initiating ERT before age 16 may decrease renal and cardiac manifestations of Fabry disease [217].

Pre-symptomatic patients can now be identified with NBS [233], but limited genotype-phenotype correlations and the abundance of unique *GLA* mutations make it nearly impossible to accurately predict disease severity or to determine the appropriate timing for ERT initiation [234]. Further, patients identified prior to symptom onset have been rarely studied [235].

In 2015, the European Fabry Working Group recommended starting ERT in patients with classic and non-classic Fabry disease immediately after early clinical signs of Fabry disease-related involvement appear; it was also recommended that treatment be considered in asymptomatic male patients older than 16 years (Class IIB recommendation) [236]. The US expert panel recommended considering treatment for boys with classic Fabry disease mutations as early as 8–10 years of age, irrespective of whether symptoms are present [237]. In 2019, experts suggested consideration of ERT initiation in asymptomatic boys with classical Fabry disease and for girls aged 7 and above who are Fabry disease heterozygotes, although no data are available for these population sub-groups [238].

Conditions requiring early symptomatic treatment

Congenital myasthenic syndromes

Congenital myasthenic syndromes (CMSs) are a group of rare inherited neuromuscular disorders resulting from mutations in genes that regulate the neuromuscular junction function [239]. The clinical presentation of CMS is diverse, encompassing varying degrees of axial and limb-girdle muscle weakness and muscle fatigability [240]. Notably, symptoms

may include weakness in ocular, facial, and bulbar muscles leading to ptosis, ophthalmoplegia, and feeding difficulties [240, 241]. Respiratory issues such as episodic apnea, and joint contractures may also be present. The onset of symptoms can occur from infancy to adulthood [242–244], although the majority of cases manifest within the first year of life [245]. Genetic diagnosis is essential for confirming CMS and over 35 genes have been identified that are associated with CMS, with pathogenic variants in the gene encoding the acetylcholine receptor subunit epsilon being the most prevalent [246]. Due to the heterogeneity of CMS, specific phenotypic manifestations and disease progression vary significantly between subtypes and even among individuals with the same genetic mutation.

There are no approved curative therapies for CMS. The choice of symptomatic therapeutic agents is determined by the underlying genetic defect. Treatment options may include acetylcholinesterase inhibitors, 3,4-diaminopyridine [247], adrenergic agonists (such as salbutamol [248], albuterol [249], and ephedrine [250]), long-lived open-channel blockers of the acetylcholine ion channel (fluoxetine and quinidine) [245], and acetazolamide. The evidence supporting symptomatic treatment in CMS primarily relies on prospective and retrospective case series [251–254], individual and familial case reports, literature reviews [245, 250, 255, 256], and practice-based consensus expert reviews and recommendations [239, 246, 257–259]. Interventional studies involving albuterol (NCT01203592) and expanded access programs for 3,4-diaminopyridine (NCT00872950, NCT03062631, NCT02189720, NCT01765140) have also been conducted. There have been recent reviews of drug efficacy in CMS patients [245, 257], but to our knowledge there have been no studies assessing the impact of treatment timing on the outcomes of CMS. It should be mentioned that initiating treatment early may be critical in certain cases, such as during life-threatening respiratory episodes or when intensive care treatment is required [259]. Genes that are associated with episodic apnea notably include *CHAT* [260, 261], *RAPSN* [262], *SCN4A* [263], *SLC5A7* [264], *CHRNE*, *CHRND*, *MYO9A*, *SLC18A3*, and *COLQ* [251]. Since symptomatic treatment may improve functional ability, quality of life, and life expectancy, avoiding treatment delay is crucial, especially considering that some of these treatments are sometimes low-cost.

Metabolic diseases

Patients with various metabolic conditions can significantly benefit from appropriate symptomatic management early in the disease course. Timely initiation of treatment is essential, as it can be life-saving in certain cases [265, 266]. Management approaches often involve supplementation with essential cofactors or specific dietary adjustments to counterbalance the underlying enzyme deficiency. These conditions include multiple acyl-CoA dehydrogenase deficiency (managed with riboflavin and coenzyme Q) [267], primary carnitine deficiency (managed with carnitine) [268], and Brown-Vialetto-Van Laere and Fazio-Londe syndromes (managed with riboflavin) [265, 269]. Some benefit, mainly due to improving effort intolerance, is obtained in carnitine palmitoyl-transferase II deficiency with a high-carbohydrate diet [266, 270].

DISCUSSION

Double-blind, randomized, placebo-controlled trials, open-label studies, systematic reviews, case reports, and expert consensus all provide evidence emphasizing the importance of early treatment in neuromuscular diseases. Nevertheless, the quality of evidence differs across diseases, and the age range recommended for initiating treatment also varies depending on the specific condition. The most compelling evidence for the benefits of early treatment exists for SMA. Treatment of pre-symptomatic SMA patients has shown remarkable and long-lasting effects on motor function in certain patient subgroups, transforming the disease from condition fatal before the age of 2 to nearly or completely normal development. Early treatment provides substantial benefits for IOPD patients as well; however, deterioration after the initial improvement remains prevalent. The ideal treatment window remains less clear for LOPD [271, 272]. Notably, due to the variability of phenotype, even within the same family, and the lack of well-defined genotype-phenotype correlations, determining the optimal treatment window is quite challenging. In Fabry disease, treatment is generally advised upon the appearance of symptoms, and initiating treatment in pre-symptomatic patients remains a debated topic, as disease course is influenced considerably by factors such as sex and age. It is important to note that the natural history of this condition involves symptoms that develop during childhood, not necessarily at birth, and that treat-

ments are only approved for patients aged 7 and above. Currently, the therapeutic window appears to be later than what is considered in SMA and Pompe disease. However, as expert recommendations shift toward early treatment initiation in patients with known later onset of symptoms, including SMA patients with four copies of *SMN2* and LOPD, it may be that early treatment will also be recommended for patients with Fabry disease. There is limited evidence supporting early intervention in DMD and CMS due to the clinical and genetic heterogeneity. However, in CMS and several metabolic conditions, early initiation of symptomatic treatment can be life-saving, and the benefits and drawbacks of early treatment should be further evaluated. Similar to SMA [15, 16], Pompe [94] and Fabry Disease [187], which have multiple robust historical cohorts as references, initiating natural history studies for these condition on a larger scale is imperative, as they are essential for enabling more accurate comparisons with treated patients and design informative clinical trials.

Initiating treatment early in infants and children has various challenges and certain considerations must be acknowledged. Firstly, early diagnosis can lead to situations where the ideal treatment strategy is unclear. In SMA, expert-based consensus updated in 2019 guides therapeutic decisions in infants diagnosed through NBS [273], but evidence supporting prompt drug administration in newborns with four copies of *SMN2* remains limited [63, 86, 274]. In LOPD, although there is evidence to support treatment upon symptom appearance, the management of pre-symptomatic patients remains contentious due to the significant costs (both economic and social), antibody development concerns, and the requirement for life-long intravenous infusions [271]. In IOPD, there is uncertainty about the optimal dose and frequency of treatment, with some evidence suggesting more favorable outcomes with higher doses or more frequent treatment [120, 122, 147]. In Fabry disease, the precise definition of what “early” means is disputed, particularly for very young patients with a wide range of possible organ involvement and for non-classic variants or variants of unknown significance with uncertain natural history.

Secondly, it is essential to recognize the significant variability in treatment response occurs and that early initiation of treatment does not guarantee notable or lasting improvement or even any response at all. As examples, classic Pompe disease remains a serious life-limiting disease despite the therapeutic options [146], and outcomes in SMA patients with one copy

of *SMN2* remain poor despite early treatment initiation.

Thirdly, therapeutic advancements are giving rise to new phenotypes. Certain disease aspects may not be adequately addressed in clinical trials. For example, in SMA, drug-modifying treatments have positively impacted survival and motor function, but concerns are emerging about bulbar, speech, and cognitive function [275], especially in SMA1 patients [276, 277]. In Pompe disease, ERT improves survival and early-life ambulation, but later manifestations may include skeletal muscle decline, cardiac arrhythmias, hearing loss, speech dysfunction, cognitive impairment, and gastrointestinal and respiratory issues [101, 278–280]. Additionally, considering that these treatments are relatively recent, the long-term effectiveness remains unclear. Close patient monitoring is vital for developing a comprehensive understanding of treatment implications and their long-term effects.

Lastly, NBS holds tremendous potential for facilitating early diagnosis and timely treatment, but screening has some caveats that should be acknowledged. For instance, NBS accuracy is well-established in SMA; however, in Pompe disease, distinguishing between IOPD and pseudodeficiency poses challenges [136], resulting in variable positive predictive values of NBS across countries [281]. Conditions characterized by genetic diversity and the continual emergence of new variants, as seen in CMS, may present challenges. This underscores the importance of comprehensive genetic testing, incorporating approaches such as whole-exome sequencing.

CONCLUSION

Early treatment in neuromuscular diseases can prevent severe complications and can be life-saving. Acting in the early stages, before extensive function loss, is clearly beneficial in SMA for example. Delaying treatment can significantly reduce its efficacy, making timing crucial for optimal results in conditions like SMA and IOPD. The ideal therapeutic window for Fabry disease requires further investigation, and the impact of early treatment in DMD is still being evaluated due to clinical heterogeneity. CMS patients can benefit from life-saving symptomatic treatment, emphasizing the importance of raising awareness about these rare conditions and the need for broad genetic testing. When considering early treatment, aspects such as response variability,

cost, and safety must be taken into account. Stronger evidence is needed to support early intervention in several conditions, but the low incidence of rare diseases poses challenges to obtaining reliable data. Systematic reviews and meta-analyses can help summarize evidence, but they have limitations and biases. Finally, NBS is a powerful tool that has the potential to revolutionize the course of diseases where early intervention is crucial.

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