Journal of Human Genetics (2019) 64:1153–1171
https://doi.org/10.1038/s10038-019-0662-9

REVIEW ARTICLE

Enzyme replacement therapy for mucopolysaccharidoses; past, present, and future

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Received: 28 May 2019 / Revised: 31 July 2019 / Accepted: 1 August 2019 / Published online: 27 August 2019

Abstract

Mucopolysaccharidoses (MPS) are a group of lysosomal storage disorders, which lack an enzyme corresponding to the specific type of MPS. Enzyme replacement therapy (ERT) has been the standard therapeutic option for some types of MPS because of the ability to start immediate treatment with feasibility and safety and to improve prognosis. There are several disadvantages for current ERT, such as limited impact to the brain and avascular cartilage, weekly or biweekly infusions lasting 4–5 h, the immune response against the infused enzyme, a short half-life, and the high cost. Clinical studies of ERT have shown limited efficacy in preventing or resolving progression in neurological, cardiovascular, and skeletal diseases. One focus is to penetrate the avascular cartilage area to at least stabilize, if not reverse, musculoskeletal diseases. Although early intervention in some types of MPS has shown improvements in the severity of skeletal dysplasia and stunted growth, this limits the desired effect of ameliorating musculoskeletal disease progression to young MPS patients. Novel ERT strategies are under development to reach the brain: (1) utilizing a fusion protein with monoclonal antibody to target a receptor on the BBB, (2) using a protein complex from plant lectin, glycan, or insulin-like growth factor 2, and (3) direct infusion across the BBB. As for MPS IVA and VI, bone-targeting ERT will be an alternative to improve therapeutic efficacy in bone and cartilage. This review summarizes the effect and limitations on current ERT for MPS and describes the new technology to overcome the obstacles of conventional ERT.

Introduction

The premise of enzyme replacement therapy (ERT) for mucopolysaccharidosis (MPS) is based on the idea of supplying the missing enzyme in circulation to reduce the amount of accumulated glycosaminoglycans (GAGs) in various tissues. However, not all ERT target the same receptor for uptake. For MPS, the infused enzyme must attach to the mannose-6-phosphate (M6P) receptors, which target uptake into lysosomes of the cell [1]. Each MPS is deficient in a specific enzyme that plays a critical role in the breakdown of the specific GAGs. The first approved ERT was not for MPS but rather, for Gaucher disease, an autosomal recessive lysosomal storage disorder (LSD) caused by a deficiency of β-glucocerebrosidase [2]. ERT for Gaucher disease does not target the M6P receptors on the cell; instead, terminal α-mannose residues are used for targeting macrophages via the mannose receptor (MR)-mediated uptake [3]. Currently, ERT is available in the United States for nine LSDs; Fabry disease, Gaucher disease, Lysosomal acid lipase deficiency, MPS I, MPS II, MPS IVA, MPS VI, MPS VII, and Pompe disease.

ERT has been shown to have systemic effects in MPS patients, such as reducing hepatosplenomegaly and urinary glycosaminoglycan (uGAG) levels, as well as increasing

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activity of daily living (ADL). Although ERT improves some clinical symptoms in each type of MPS, most ERT had a limited effect on CNS, corneal clouding, valvular heart disease, and skeletal deformities. These areas, because of a barrier or avascularity, need to be addressed in the new generation of ERT.

Decreased pulmonary function in MPS patients can be attributed to upper airway narrowing due to hypertrophied upper airway structures (large tongue, adenoid, and tonsil), excessively long U-shaped trachea, tracheal narrowing, lower airway GAG deposits, and decreased thoracic dimensions (restrictive lung) from skeletal dysplasia, and short stature [4, 5]. Especially in patients with MPS IVA, the restrictive and obstructive lung is due to an imbalance of growth anatomically (trachea and vessels grow while the spine and thoracic bones stop growing), leading to the life-threatening issue. ERT cannot normalize bone deformity in the spine, ribs, and sternum, causing a decreased and crowded thoracic cavity that cannot accommodate the trachea, vessels, and upper airway structures adequately. Therefore, ERT may provide a limited impact on pulmonary function due to the remaining issue of skeletal dysplasia (restrictive lung). The recent long-term study of MPS IVA with ERT has shown that there was a global reduction in static spirometry values in all subjects with ERT, as well as cardiorespiratory function as assessed by the 6MWT [6]. Cardiovascular pathology in MPS appears most commonly as coronary artery narrowing and valve thickening resulting in regurgitation [7]. In MPS patients, GAG accumulation in the avascular valves, myocardium, coronaries, and aorta may cause cardiovascular pathology, including valve regurgitation, myocardial hypertrophy, and coronary artery disease [7]. Valve regurgitation, coronary artery disease, and weak pulmonary function may lead to cardiomegaly, which may perpetuate cardiovascular disease in MPS patients [8]. ERT may decrease GAG accumulation in heart muscle to some extent if treatment initiated early in life, but it remains unresolved in avascular heart valves.

For most cases, patients do not develop IgE antibodies that cause anaphylactic reactions, and antidrug antibodies (ADAs) usually do not correlate with clinical efficacy. However, patients should still be monitored and treated for serious adverse events (AE).

Conventional ERT cannot cross the blood–brain barrier (BBB), so that the new types of ERT to penetrate the BBB are under clinical trials for MPS I, II, IIIA, and IIIB, some of which use a monoclonal antibody (MAb) attached to the enzyme, which functions as a vehicle to bypass the BBB [9–13]. Another method to penetrate the BBB is to change the administration route, via IT or Intracerebroventricular (ICV) (Fig. 1); however, clinical trials of IT ERT for MPS I, MPS II, and MPS IIIA did not demonstrate therapeutic efficacy and have been discontinued [14–16]. Clinical trial in MPS IIIB involving ICV is ongoing [17]. Bone-targeting ERT for MPS IVA is evaluated preclinically in MPS IVA mice [18].

In this article, we review and summarize benefits and detriments of current ERTs and novel ERTs (Tables 1–6) to improve the unmet challenges.

Conventional ERT

MPS I

The approved ERT for MPS I is a recombinant human α-l-iduronidase, also called laronidase. Laronidase has shown improvement of endurance, the apnea/hypopnea index, and ADL [19]. ERT provides a limited impact on cardiovascular and/or bone pathology [20–23] and does not improve neurological function despite the age of starting infusions [21]. Concerning safety, no consistent relationship was observed between ADAs titers and hypersensitivity, enzyme uptake, or clinical efficacy results [23]. Although most treated patients developed ADAs, few patients who had allergic reactions were positive for IgE [19, 23]. As ADA titers increased, the percent reduction in uGAG levels decreased, suggesting that high ADA titers can affect a clinical endpoint [23]. Thus, laronidase is relatively safe, but inhibition of enzyme uptake may occur with elevated neutralizing ADAs [22, 23].

MPS I patients also display short stature at ~2 years old, when the height velocity decreased [24]. Although ERT has no effect on growth and is not commonly evaluated, hematopoietic stem cell therapy (HSCT) can maintain linear growth for a period of time [25]. However, patients with HSCT still tend to fall below 1 or 2 standard deviations compared with age-matched controls [25, 26].

To reach the CNS and cardiovascular systems, a high dose of laronidase has been tested in a mouse model. Adult MPS I mice had 97% of normal enzyme activity levels in cerebrum, coupled with improved learning, and increased enzyme activity to supranormal levels in the heart [5].

MPS II

There are two approved ERTs for MPS II. The first approved ERT uses a recombinant human iduronate-2-sulfatase (rhIDS), also called idursulfase [27]. Idursulfase has shown to improve endurance, increased joint ROM, stimulated minimal growth, increased absolute increased forced vital capacity (FVC), and improved quality of life [27, 28]. Currently, a phase IV study on the long-term effects of 0.5 mg/kg via IV idursulfase on height and weight for patients <6 years of age is ongoing [29].

Another ERT also uses the rhIDS, idursulfase beta, also called Hunterase. However, idursulfase beta comes from the chinese hamster ovary (CHO) cell line, while idursulfase is

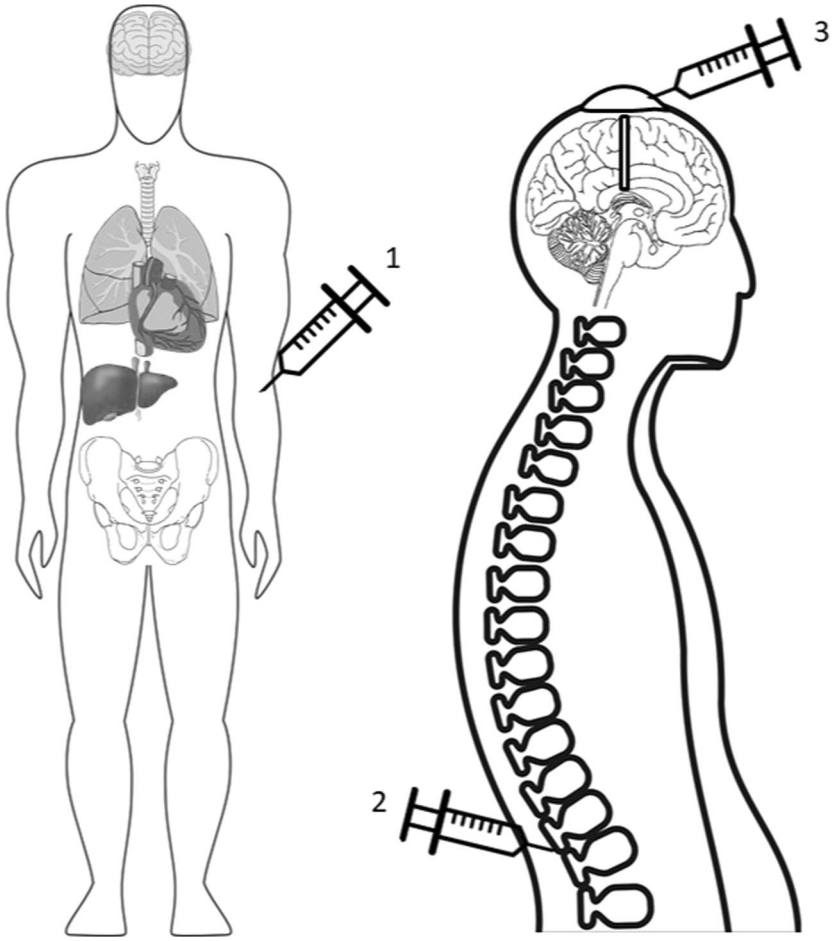

Fig. 1 ERT administration via (1) intravenous, (2) intrathecal, and (3) intracerebroventricular via Ommaya reservoir administration. Intrathecal and intracerebroventricular may implant a drug-delivery device, as depicted in 3, instead of performing injections. Target systems for ERT are the central nervous system, pulmonary system, cardiovascular system, liver, and musculoskeletal system. However, the effects of ERT on these systems vary

from the human fibrosarcoma cell line. Both enzymes have the same amino acids, but idursulfase beta provides a faster uptake into fibroblasts, which could contribute to a milder immune response because the enzyme spends less time in the bloodstream [30]. Another study showed no clinically significant impact in developmental milestones using the Denver developmental screening test II but showed an increase of the height and weight comparable with the normal growth curve [31], a decrease of uGAGs, and improvement of endurance and joint ROM [32].

In natural growth, MPS II patients developed short stature by 8 years old [33, 34]. ERT has demonstrated an improved growth velocity, with no difference in velocity between patients who started ERT before puberty (8–11 years old) and patients who started ERT after puberty (12–15 years old) [35]. However, the growth in MPS II patients may remain within normal range only when the initiation of ERT is under 10 years of age [36]. Conventional ERT for MPS II patients provides little effect on the brain and cardiovascular pathology [37, 38].

Another issue is the presence of antibodies, which can limit the effects of ERT [39]. ADAs developed in most patients, but no IgE antibodies were detected [32]. The presence of ADAs has decreased the efficacy of the drug tested via uGAG levels and pulmonary function [28]. High ADA titers correlated with high uGAG levels and lower absolute FVC but not with AEs [28, 40, 41]. In 2017, Kubaski et al. reported that HSCT eliminated immune response with ERT and showed clinical improvement of hepatomegaly and ADL [42].

MPS III

The phase I/II clinical trial for MPS IIIB included varying doses (1 mg/kg every other week, then 3 mg/kg every other week) via IV of recombinant human α-N-acetylglucosaminidase (rhNAGLU) [43]. The dose of 3 mg/kg every other week had a 26.3% mean reduction from baseline of total HS in CSF [44]. The therapeutic effect was not confirmed. The development of IV ERT for MPS IIIB was halted before passing phase II clinical trials in 2017 [45].

MPS IVA

In 2014, ERT for MPS IVA using recombinant human N-acetylgalactosamine 6-sulfatase (rhGALNS), referred to as

Table 1 MPS I ERT status

Product	Organization	Description	Route	Dose	Status	Eligibility	Clinical endpoint	Website	Refs
Laronidase	Biomarin/Sanofi Genzyme	rhIDUA	IV	0.58 mg/kg weekly	Approved	(For Phase III completed) ≥5 years old. 6MWT minimum 5 m. No bone marrow transplant or tracheostomy.	FVC. 6MWT. Apnea/Hyponea. Liver Volume. Visual acuity. CHAQ/HAQ-DI score. Active joint ROM. uGAG Levels.	http://www.aldurazyme.com/patients.aspx	NCT00258011
AGT-181	ArmaGen Technologies	HIR-MAb with IDUA fusion protein	IV	1, 3, or 6 mg/kg weekly	Phase II Ongoing. Expected to finish in July, report full results in August. Children in Phase II Extension Ongoing	2+ years old. Hurler–Scheie or Scheie syndrome. No successful HSCT or major organ transplant. No investigational drug in 1 year prior to administration. Must discontinue ERT for 1 week prior dosing and during study duration.	Adverse events. Change in total uGAG levels, urinary HS levels, plasma HS and DS, CSF HS, and DS. Change in liver or spleen volume via MRI.	http://armagen.com/our-pipeline/clinical-trials/	NCT03071341
Laronidase-IT for Cognitive Decline	Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center	Laronidase ERT	IT	1.74 mg IT every 3 months	Completed. Enrolling in extension study by invitation	6+ years old. No HSCT.	Hopkins Verbal Learning Test.	NA	NCT00852358 Extension study: NCT02232477
Plant Lectin RTB	BioStrategies LC	Plant lectin RTB protein with IDUA	IV	5.8 mg/kg weekly	Preclinical	NA	NA	http://www.biostrategies-lc.com/mps1.html	No clinical trial
JR-171	JCR Pharmaceuticals Co., Ltd	Transferrin receptor MAb with IDUA fusion protein	IV	NA	Preclinical	NA	NA	http://www.jcrpharm.co.jp/en/site/en/biopharmaceutical/product.html	No clinical trial
PLGA Nanoparticles	Unimore; University of Modena and Reggio Emilia	Poly-lactide-co-glycolide nanoparticles modified with G7; ERT	IV	2 mg nanoparticles, 0.2 mg/animal of albumin	Preclinical	NA	NA	NA	No clinical trial
Laronidase with Stem Cell Transplant	Masonic Cancer Center, University of Minnesota	Laronidase ERT before and after stem cell transplant	IV	0.58 mg/kg weekly	Phase II Completed. Second study terminated	Up to 7 years old. Candidates for first HSCT. No previous administration of laronidase. Second study had all age groups.	Survival and use of ventilator support. Donor engraftment. Grades III–IV acute GvHD. GAG levels. Adverse events. Development of ADAs in serum. Improvement of Obstructive Apnea by Polysomnography.	NA	NCT00176891 Second study: NCT01572636
Laronidase-IT for Spinal Cord Compression	Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center	Laronidase ERT	IT	(0.58 mg/ml solution for IV) 1.74 mg IT monthly	Phase I (Discontinued due to slow enrollment)	8+ years old. Hurler–Scheie, Scheie, or Hurler after 2 years of HSCT. Spinal cord compression.	Blood and CSF tests. Spinal cord compression improvement.	NA	NCT00215527

6MWT 6 min walk test, *ADA* antidrug antibodies, *CHAQ/HAQ-DI* Child Health Assessment Questionnaire/Health Assessment Questionnaire-Disability Index, *CSF* cerebrospinal fluid, *ERT* enzyme replacement therapy, *G7* 7-amino acid glycopeptide, *GvHD* graft vs host disease, *HIR-MAb* human insulin receptor monoclonal antibody, *HSCT* hematopoietic stem cell therapy, *IDUA* α-l-iduronidase, *IT* intrathecal, *IV* intravenous, *MAb* monoclonal antibody, *NA* not available, *rhIDUA* recombinant human α-l-iduronidase, *ROM* range of motion, *UCLA* University of California Los Angeles, *uGAG* urinary glycosaminoglycan

Table 2 MPS II ERT status

Product	Organization	Description	Route	Dose	Status	Eligibility	Clinical endpoint	Website	Refs
Idursulfase-IV	Shire Pharmaceuticals	rhIDS	IV	0.5 mg/kg weekly	Approved	Phase II/III: 5–31 years old.	6MWT. FVC. uGAG levels. Liver and spleen volume.	http://www.elaprase.com/hcp/about/	NCT00069641
Idursulfase Beta-IV	Green Cross Corporation	Idursulfase Beta ERT	IV	0.5 mg/kg weekly	Approved in Korea	All ages.	Adverse events. Vital signs, physical and clinical examinations. Anti-IDS-beta status. uGAG levels. 6MWT.	http://www.globalgreencross.com/product/list_detail?p_idx=36	NCT01645189 Extension study: NCT02044692
JR-141	JCR Pharmaceuticals Co., Ltd	Transferrin receptor MAb with IDS fusion protein	IV	2.0 mg/kg weekly	Phase II/III ongoing	Males any age. No previous HSCT. No previous ERT or willing to interrupt current treatment for a least 1 week before study infusion.	CSF HS and DS. Serum HS and DS. Urine HS and DS. Liver and spleen volumes. Cardiac function. 6MWT. Joint ROM. Neurocognitive testing.	http://www.jcrpharm.co.jp/en/site/en/biopharmaceutical/product.html	NCT03568175
AGT-182	ArmaGen Technologies	HIR-MAb with IDS fusion protein	IV	1.0 mg/kg or 3.0 mg/kg weekly	Phase I completed	18+ year old males. Discontinue ERT or no ERT for 3 months prior and elevated uGAGs 3.5 times normal or never had ERT. No investigational drugs 90 days prior administration.	Adverse events. Concentration, half-life, area under the curve, mean residence time, volume of distribution and clearance of AGT-182. uGAGs, CSF GAGs, and plasma GAGs. Liver and spleen size.	http://armagen.com/our-pipeline/clinical-trials/	NCT02262338
Idursulfase Beta-ICV	Green Cross Corporation	Idursulfase Beta ERT	ICV	NA	Phase I/II ongoing	NA	NA	http://www.globalgreencross.com/rd/pipeline#none	NA
PLGA Nanoparticles	Unimore; University of Modena and Reggio Emilia	Poly-lactide-co-glycolide nanoparticles modified with G7; ERT	IV	2 mg nanoparticles, 0.2 mg/animal of albumin	Preclinical	NA	NA	NA	No clinical trials
Idursulfase-IT: HGT-HIT-094	Shire Pharmaceuticals	rhIDS	IT	10 mg monthly	Phase III (discontinued): failed to meet the main and secondary goals of a late-stage clinical trial	Controlled, randomized, two-arm, open-label, assessor-blinded, multicenter study monthly idursulfase-IT 10 mg for 12 months in pediatric male patients. ≥3 and <18 years of age.	Adverse events. Enzyme activity in CSF and serum. CSF and urine GAGs. CSF and serum ADAs. DAS-II. BSID-III. DQ. VABS-II. MRI for brain structure volume.	http://www.elaprase.com/hcp/about/	NCT02412787

6MWT 6 min walk test, *ADA* antidrug antibodies, *BSID-III* Bayley Scales of Infant Development, Third Edition, *CSF* cerebrospinal fluid, *DAS-II* Differential Ability Scales, Second Edition, *DQ* developmental quotient, *DS* dermatan sulfate, ERT enzyme replacement therapy, *FVC* forced vital capacity, *G7* 7-amino acid glycopeptide, *GAG* glycosaminoglycan, *HIR-MAb* human insulin receptor monoclonal antibody, *HS* heparan sulfate, *HSCT* hematopoietic stem cell therapy, *ICV* intracerebroventricular, *IDS* iduronate-2-sulfatase, *IT* intrathecal, *IV* intravenous, *MAb* monoclonal antibody, *MRI* magnetic resonance imaging, *NA* not available, *rhIDS* recombinant human iduronate-2-sulfatase, *ROM* range of motion, *uGAG* urinary glycosaminoglycan, *VABS-II* Vineland Adaptive Behavior Scales, Second Edition

Table 3 MPS III ERT status

MPS III type	Product	Organization	Description	Route	Dose	Status	Eligibility	Clinical endpoint	Website	Refs
A	SOBI-003	SOBI	Modified sulfamidase using proprietary glycan modification technology to extend half-life to enable CNS penetration	IV	3 mg/kg weekly	Phase I/II ongoing	12–72 months. Diagnosed MPS IIIA from mutation. Medically stable. No previous treatment.	Adverse events. Serum, CSF, and urine HS. Neurocognitive development quotient using BSID-III or KABC-II. VABS-II. Pediatric quality of life.	http://www.sobi.com/Pipeline/Development-pipeline/SOBI003/	NCT03423186
A	RTB Lectin and SGSH	BioStrategies LC	RTB lectin protein with SGSH	IV	NA	Preclinical	NA	NA	http://www.biostrategies-lc.com/mps3.html	No clinical trials
A	AGT-184	ArmaGen Technologies	HIR-MAb with SGSH fusion protein	IV	19 μm/kg in rhesus monkey	Preclinical	NA	NA	http://armagen.com/our-focus/sanfilippo-a-syndrome/	No clinical trials
A	SHP610	Shire Pharmaceuticals	rhHNS	IT	45 mg every 2 or 4 weeks	Phase II completed (discontinued)	12–48 months old. No HSC or bone marrow transplant. No gene therapy.	BSID-III and adverse events. Serum ADAs. VABS-II. Total cortical gray matter volume. CSF, GAGs, and uGAGs. rhHNS in CSF and serum.	https://www.shire.com/research-and-development/pipeline	NCT02350816
B	BMN 250	BioMarin	rhNAGLU with IGF2	ICV	Up to 30, 100, or 300 mg escalating doses weekly	Phase I/II	1–10 years old. No stem cell, gene therapy of ERT.	Adverse events. DQ. Concentration of drug in CSF and plasma. Total antidrug antibody in CSF and serum. GAG levels in CSF, plasma, and urine. Brain structure by MRI.	http://www.biomarin.com/products/clinical-trials/mps-iiib/	NCT02754076
B	AGT-187	ArmaGen Technologies	HIR-MAb with rhNAGLU fusion protein	IV	NA	Preclinical	NA	NA	http://armagen.com/compounds/agt-187-sanfilippo-b-syndrome/	No clinical trials
B	SBC-103	Alexion	rhNAGLU	IV	1 mg/kg every other week, then 3 mg/kg every other week	Phase I/II (discontinued)	2–12 years old. No gene therapy. No HSC or bone marrow transplant.	Physical examinations. Vital signs. ECG. Concomitant medications. Antidrug antibodies. Neurocognitive and developmental function. Brain structure volumetric assessment. BBB integrity.	http://www.alexion.com/default.aspx	NCT02618512
D	rhGNS	Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center and Phoenix Nest Inc.	rhGNS	IT	NA	Preclinical	NA	NA	https://labiomed.org/news/phoenix-nest-and-la-biomed-receive-over-1-7-million-to-develop-treatments-for-devastating	No clinical trials

ADA antidrug antibodies, *BBB* blood–brain barrier, *BSID-III* Bayley Scales of Infant Development, Third Edition, *CSF* cerebrospinal fluid, *DQ* developmental quotient, *ECG* electrocardiogram, *ERT* enzyme replacement therapy, *GAG* glycosaminoglycan, *HIR-MAb* human insulin receptor monoclonal antibody, *HS* heparan sulfate, *HSC* hematopoietic stem cell, *ICV* intracerebroventricular, *IT* intrathecal, *IV* intravenous, *KABC-II* Kaufman Assessment Battery for Children, Second Edition, *MRI* magnetic resonance imaging, *NA* not available, *rhHNS* recombinant human heparan N-sulfatase, *rhNAGLU* recombinant human α-N-acetylglucosaminidase, *SGSH* sulfamidase, *UCLA* University of California Los Angeles, *uGAG* urinary glycosaminoglycan, *VABS-II* Vineland Adaptive Behavior Scales, Second Edition

Table 4 MPS IVA ERT status

Product	Organization	Description	Route	Dose	Status	Eligibility	Clinical endpoint	Website	Refs
Elosulfase alfa	BioMarin	rhGALNS	IV	2.0 mg/kg weekly	Approved	(For Phase III completed) ≥5 years old. No HSCT. Average 6MWT distance 30–325 m.	6MWT. 3MSC. Urinary KS levels.	http://www.vimizim.com/	NCT01275066 Extension study: NCT01415427

3MSCT 3 min stair climb test, *6MWT* 6 min walk test, *HSCT* hematopoietic stem cell therapy, *KS* keratan sulfate, *rhGALNS* recombinant human N-acetylgalactosamine 6-sulfatase

Table 5 MPS VI ERT status

Product	Organization	Description	Route	Dose	Status	Eligibility	Clinical endpoint	Website	Refs
Galsulfase	BioMarin	rhARSB	IV	1 mg/kg weekly	Approved	(For Phase III completed) ≥7 years old. No pregnancy. Able to walk independently for 5–270 m in 6 min or ≤400 m in 12 min.	12MWT. 6MWT. uGAG levels.	http://www.naglazyme.com/	NCT00067470 Extension study: NCT00104234

6MWT 6 min walk test, *12MWT* 12 min walk test, *rhARSB* recombinant human arylsulfatase B, *uGAG* urinary glycosaminoglycan

Table 6 MPS VII ERT status

Product	Organization	Description	Route	Dose	Status	Eligibility	Clinical endpoint	Website	Refs
Vestronidase alfa	Ultragenyx	rhGUS	IV	4 mg/kg weekly	Approved	5–35 years old. No successful bone marrow or stem cell transplant.	Change in uGAG levels. Adverse events. Individualized clinical response. % predicted FVC. MVV. Uncorrected visual acuity. 6MWT. Shoulder flexion. Fine/gross motor function. Pediatric Quality of Life Multidimensional Fatigue Scale.	http://www.ultragenyx.com/pipeline/rhGUS/	NCT02230566 Extension study: NCT02432144

6MWT 6 min walk test, *FVC* forced vital capacity, *MVV* maximum ventilatory ventilation, *rhGUS*, recombinant human β-glucuronidase, *uGAG*, urinary glycosaminoglycan

elosulfase alfa, has been approved. Elosulfase alfa improved endurance, stabilized FVC, and forced expiratory volume in 1 s, decreased left ventricular mass index, and showed no changes in mobility [46–51]. For patients with the severe phenotype, their mitral insufficiency, aortic insufficiency, spinal abnormalities, or corneal clouding did not improve [51]. During ERT, keratan sulfate (KS) level in blood remained unchanged in spite of urine KS reduction [52].

ADAs developed in most patients, but there was no correlation between the presence of ADAs and efficacy measurements, the presence of AE, or severity of AE [47, 48, 53]. Only a small number of patients are positive for IgE [47, 48, 53].

Until now, ERT for MPS IVA provides little impact on bone pathology in human patients as described in affected mice [50, 52, 54–59]. To improve bone pathology, bone-targeting ERT should be considered for MPS IVA with the early intervention [56]. There was little improvement in bone pathology in surgical remnants from patients treated with ERT [50, 55–59]. In 2015, Hendriksz et al. described little impact on growth in patients over 5 years of age in phase III trial for 24 weeks [49]. In 2015, Jones et al. described the growth in MPS IVA patients under 5 years of age with one year of ERT, suggesting that there is a trend toward improvement in growth without clear proof and that a long-term observation is required [60, 61]. It is notable that these data did not compare with the natural Morquio A growth chart. In 2016, Cao et al. indicated that early ERT starting at 21 months did not improve the bone outcome in a severe MPS IVA patient, as determined after the 30 month-long treatment [50]. The height of this patient increased during the first year of the ERT, but no more height gain was observed for 18 months. Bone deformities worsened, and his medullar cervical spine compression showed no improvement, requiring decompression surgery. These findings in our study were compatible with this result. Our recent study on 12 patients starting ERT under 5 years was consistent with this case. We have confirmed the shorter final height in 6 of 12 patients under 5 years with the follow-up of at least 2 years of ERT, and the other five patients, except one with an attenuated form, had marked slow growth velocity [62]. It is critical to use the Morquio A growth chart as a natural history in comparison, which provides a more precise assessment of the growth impact. Further studies with larger sample sizes and/or patients treated under 2 years of age are needed to evaluate whether IV ERT can improve the growth of MPS IVA patients. In conclusion, the affected children treated with ERT still exhibit poor growth. Until now, there has been no proof that the current ERT improves bone lesion in MPS IVA patients.

In 2019, Kenth et al. reported long-term respiratory changes in patients with MPS IVA treated with ERT [6]. Overall, they have demonstrated a global decline in spirometry variables and improvement post adeno-tonsillectomy, albeit the overall result being a decline in function. Noninvasive ventilation and adenotonsillectomy suggested more effective in the ERT group, either improving pulmonary function or attenuating deterioration.

Another approach involves the clearance of KS and CS from the extracellular matrix (ECM) in cartilage [63]. Skeletal deformities are caused by epiphyseal chondrocyte dysfunction [64]. The earliest pathogenic sign in MPS VIA patients may be impaired regression of cartilage canals within epiphyses and epiphyseal-type bones [65]. The long bones grow bidirectionally by reabsorption and formation of areas except for the most superficial layer, so that this may suggest that waste accumulation in macrophages within cartilage canals are more important than lysosomal storage in chondrocytes [65]. In addition, MPS IVA patients may have increased the levels of proinflammatory and prooxidant biomarkers in blood, contributing to widespread cell DNA damage [65, 66]. Overall, the role of ECM for bone growth is important, but the mechanism of disruption of ECM by storage materials remains unknown, and the removal of storage materials in ECM remains an unmet challenge.

MPS VI

The approved therapy for MPS VI is a recombinant human arylsulfatase B, referred to as galsulfase. Galsulfase improves endurance, improves pulmonary function, decreases uGAG levels, and increases body mass indexes but does not affect cardiovascular function [67–71]. With younger patients, cardiovascular pathology may be prevented [72], but usually, there is a stabilization of cardiac function when treatment starts after cardiac pathology begins [67, 73, 74]. Deaths were often due to cardiovascular or pulmonary dysfunctions, which prioritize these systems as targets for ERT [50, 67].

The progression of bone pathology (joint mobility, skeletal deformity, short stature) cannot be reversed at any age, only slowed with ERT [74, 75]. If ERT is initiated before the development of dysmorphism in facial features or hearing impairment, these symptoms can be stalled, but corneal clouding cannot be avoided [75]. MPS VI patients show short stature around 2 years, and severe phenotypes present end the height lower than the 5th percentile of normal controls by 4–7 years [76]. Attenuated patients increase the height at a faster rate but still demonstrate final heights at a range from the 50th percentile to below the 5th percentile of normal controls [76]. After ERT, approximately half of the patients younger than 5 years old fell below the original percentile curve, while 38% remained in the same growth curve [77]. Most final heights fell at the 50th percentile or below of normal control growth curve

[77]. Thus, early ERT may increase growth rates but still cannot normalize patients' height.

Only a few patients experience an anaphylaxis event, but it is not correlated with the presence of IgE [53]. Studies with patients of varying disease severity demonstrated that high levels of neutralizing ADAs in blood could inhibit enzyme uptake by the cell in vitro, but that ADAs do not affect clinical efficacy [78, 79]. Reversely, in high and low ADA titer mice, the enzyme distribution differs, suggesting that ADAs may affect efficacy [80, 81].

Overall, ERT for MPS VI has limited efficacy on bone and cardiovascular pathology, especially when symptoms are already present. Early intervention is critical for improving prognosis.

MPS VII

In 2017, ERT for MPS VII was approved by using recombinant human β-glucuronidase (rhGUS), also known as vestronidase alfa [4]. Preclinical studies have focused on hard-to-reach areas such as the heart, brain, and bones. ERT has shown to resolve mitral valve regurgitation in MPS VII neonatal dogs [82]. Another study in MPS VII mice used rhGUS purified with sodium metaperiodate and sodium borohydride to inactivate the M6P recognition markers [83]. This chemically modified rhGUS showed a prolonged half-life in plasma circulation (18.5 h), compared with unmodified rhGUS (11.7 min) [83]. Using a dose of 4 mg/kg via IV weekly, there were increased enzyme levels in the brain (7.2% of wild type), heart, and lungs resulting in substantial improvement of GAG storage in hippocampal and neocortical neurons, compared with the same dose of conventional rhGUS [83]. Perhaps targeting an alternate route of M6P receptors could cross the BBB in adequate amounts to affect neuropathy.

To target the bone, one preclinical study tagged a short peptide consisting of acidic amino acids to rhGUS [84]. After 12 weekly infusions via IV of the tagged enzyme, it was delivered to the bone, bone marrow, and brain in MPS VII mice [84]. The enzyme also reversed storage pathology and reduced storage in cortical neurons, hippocampus, and glia cells [84].

A phase III clinical trial showed that most patients developed ADAs, but ADAs did not correlate with hypersensitivity events or urine dermatan sulfate levels [85, 86]. Furthermore, an interim report from the long-term extension study up to 144 weeks stated that patients uGAG levels declined and that 6MWT distance improved [86]. In a case study, a 5-month old patient was given a biweekly 4 mg/kg rhGUS via IV administration because of presentation of severe MPS VII, including respiratory insufficiency requiring tracheostomy and mechanical ventilation, absent vocalizations, and mild tricuspid insufficiency [87]. The infant showed the improvement of pulmonary function, sound recognition, grasping, and mitral regurgitation [87]. No infusion-related associated reactions have occurred with the infant [87].

Overall, the drug is safe, but more clinical trials are needed to determine the effect of high titers of ADAs on clinical efficacy and hypersensitivity reactions and to evaluate the impact on the skeletal, cardiovascular, and CNS involvement.

Overall impact and limit

In general, approved ERTs reduced uGAG levels, improved endurance tests, and decreased hepatosplenomegaly with limited improvements in pulmonary function, joint mobility, and cardiovascular pathology. Furthermore, ERT does not affect CNS impairment and existing and progressive skeletal dysplasia, both of which often progress despite therapy. Although ERT may provide mild improvements in pulmonary function to some extent, ERT cannot normalize it because of preexisting skeletal dysplasia with the restrictive thoracic cavity and consequently, the limitation of maximum vital capacity [28]. ERT at an early age provides more effect to pulmonary function for MPS types with minimal CNS involvement and mild skeletal dysplasia. More severe types of MPS may require additional surgical interventions, such as a tracheostomy, trachea reconstruction, or-more recently-tracheal stenting [88, 89].

Novel ERT

Fusion protein

Since the primary obstacle that hinders conventional ERT is bypassing the BBB, there have been several strategies to deliver the enzyme to the brain. One method is fusing the recombinant human enzyme for a specific type of MPS to a MAb. The BBB has receptors that interact with the antibody and allow the antibody to cross. Ideally, the antibody would carry the enzyme across the BBB and increase enzyme activity in the brain. The benefit of this method is that the treatment can use a more feasible noninvasive administration via IV [90].

Antihuman insulin receptor antibody

One current developing therapy uses the insulin receptor. This fusion protein uses a MAb, bound to the enzyme which interacts with the human insulin receptor (HIR) located on the BBB. The MAb and enzyme fusion protein penetrates the BBB in adult Rhesus monkeys after IV administration [91]. The enzyme would then interact with brain cells, such as neurons and glial cells, normally via

HIR on the cell membrane [91]. Rhesus monkeys treated with HIR-MAb and IDUA fusion protein showed that more HIR-MAb/IDUA entered the brain compared with unmodified IDUA [92]. Both IDUA and HIR-MAb/IDUA were delivered to the peripheral organs in similar concentrations, suggesting that HIR-MAb/IDUA enzyme can impact visceral organs as well [92]. However, both IDUA enzymes provided low enzyme activity in CSF (0.11% ID/100 g for IDUA and 0.22% ID/100 g for HIR-MAb/IDUA), which may indicate that this dose does not allow to deliver sufficient amounts of enzyme distribution to CNS [92]. It is of great interest to measure the enzyme activity level in CSF as well since for a trans-BBB enzyme, the distribution into cells could far outpace the secretion of the protein into CSF. Their current clinical trial for MPS I uses an enzyme called AGT-181, or valanafusp alpha, administered weekly via IV to 21 patients at 2 years and older with varying dose levels (0.3, 1.0, or 3.0 mg/kg for adults; 1.0, 3.0, and 6.0 or 9.0 mg/kg for children) [93]. High titer ADAs do not change plasma clearance of AGT-181 [94]. Furthermore, few patients had an infusion-related reaction, but more research is needed for establishing the relationship between ADA or IgE antibodies and the clinical efficacy [94, 95]. ADAs titers were stabilized or decreased during treatment [95]. ERT stabilized uGAGs, reduced liver and spleen volume, increased shoulder flexion, stabilized cognitive development quotient (DQ), and seldom provided infusion-related reactions [96].

As for MPS II, their current phase I clinical trial administers HIR-MAb/IDS via IV to adult patients weekly at either 1.0 mg/kg or 3.0 mg/kg [11]. The development for MPS IIIA and IIIB are both in the preclinical stages. In Rhesus monkeys with MPS IIIA or IIIB, the appropriate fusion protein has demonstrated passing the BBB at around 1% injected dose/brain [12, 97].

Antihuman transferrin receptor antibody

Another fusion protein for MPS I and II is JR-171 and JR-141, respectively, targeting the transferrin receptor (hTfR), which carries transferrin bound to iron, on the BBB. This technology also claims to penetrate the BBB using an hTfR-MAb fused with IDUA for MPS I or IDS for MPS II. The MAb and enzyme fusion protein interacts with the hTfR on the BBB and penetrates the barrier [98].

In MPS II mice, a 3 mg/kg IV injection of hTfR-MAb/IDS normalized GAG levels in the peripheral tissues of organs and in the brain [98]. In wild-type monkeys, IV injection with a 5 mg/kg dose has shown the presence of the enzyme in the brain and spinal cord [98]. This shows the ability of the fusion protein to reach the CNS [99]. In phase I/II clinical trial, the drug has only caused mild AE in adult MPS II patients when assessing for safety [100]. All patients reduced CSF HS concentration, and none increased in ADA titers compared with the baseline [100]. Patients self-evaluated their improvements, such as one reported a new ability to skip [100]. However, there was no neurocognitive or neurodevelopmental assessment due to a short time frame [100]. The sequential phase II/III trial for MPS II administers 2.0 mg/kg or 4.0 mg/kg weekly [10]. However, there is no placebo control group for these clinical trials.

The hTfR-MAb/IDUA product is currently in the preclinical stages for MPS I.

Modified protein

Plant lectin

Another approach is to fuse the IDUA or SGSH enzymes for MPS I and IIIA, respectively, to a plant lectin to deliver the enzyme to the brain. Plant lectin ricin B chain (RTB) from *Ricinus communis* was fused with human enzyme. This fusion protein retained lectin selectivity and enzyme activity, reduced GAG accumulation in human fibroblasts, depended on sugar-binding and lectin-mediated endocytosis, and acted independently of high MMR and M6P receptors [101]. Preclinical studies of this protein administered via IV on MPS I mice showed GAG reduction in the cerebellum, heart, kidney, spleen, and liver [102]. This supports the therapy's ability to transverse the BBB and promotes enzyme activity in crucial areas, such as the heart and brain, unlike conventional ERT. Treated MPS I mice had equal or higher IDUA activities in the spleen, heart, liver, and kidneys of the normal mice [103]. The mice improved learning to escape a maze, as evaluated using the Barnes maze test, equally as well as wild-type mice [103]. Antibodies detected were against IDUA enzyme instead of the RTB complex, and there were AE following enzyme infusion [103]. Therefore, plant lectin RTB fusion protein can reduce GAG storage, affect cognitive learning, and produce ADAs. More preclinical trials on large animal models would be necessary to further solidify the safety and effects [104].

Glycan modification

Another novel ERT for MPS IIIA includes a variant of recombinant human sulfamidase (rhSGSH) using proprietary glycan modification technology to extend the half-life of rhSGSH and to pass BBB [101]. A multiple-dose, multicenter, open-label, noncontrolled phase I/II clinical trial is recruiting [101]. The clinical trial plans to have patients age 1–6 years with dose cohorts at 3 mg/kg, 10 mg/kg, or another dose undecided administered weekly via IV [105].

Insulin-like growth factor 2

For MPS IIIB, rhNAGLU fused with a peptide derived from insulin-like growth factor 2 (IGF2) is used to induce endocytosis via the M6P receptor [106]. rhNAGLU produced from CHO cells lacks M6P, which induces receptor-mediated endocytosis to target lysosomes [107]. IGF2 is a natural ligand for M6P, increases fibroblast lysosome uptake, decreases GAG storage more than just rhNAGLU alone [107, 108]. Clinical trials of ERT using recombinant NAGLU-IGF2 are now underway in the United States and Europe [109]. Preliminary results showed a reduction in HS level of CSF and preservation of cognitive function in several patients [110]. However, this approach may not be ideal. While typically the IGF2-receptor binding site is not included in the fusion construct, nevertheless the peptide retains some IGF2-receptor binding capability, which could, in theory, cause adverse effects. Fusion proteins may also be immunogenic. Pompe disease patients in a recent clinical trial involving recombinant acid alpha-glucosidase fused to an IGF2 peptide experienced hypoglycemia and immunological reactions in some subjects. Low secretion of NAGLU-IGF2 may lead to higher production costs [111]. In preclinical trials, MPS IIIB mice were injected via ICV four times over 2 weeks with various doses, and HS level was normalized in brain and liver [106, 112]. The IGF2-tagged enzyme has also demonstrated cellular uptake in mice neurons and astrocytes [113]. The ongoing phase II clinical trial includes children (1–10 years old) who receive up to three escalating doses of the drug at 30, 100, and 300 mg via ICV over 4 weeks each weekly [17]. Thus far, HS level in CSF dropped to the normal range after 1–3 doses, liver and spleen sizes normalized, and DQ stabilized or improved in most patients [114]. There have been 13 device-related AE, two of them being severe AE, indicating that the methods of administration and the drug are generally safe [114].

PLGA nanoparticles

For MPS I and II, PLGA nanoparticles modified with 7-amino acid glycopeptide, ideally, carries the corresponding enzyme to cross the BBB [115]. The concept has been tested using albumin-fluorescein isothiocyanate conjugate (FITC), which is derived from bovine, as the model drug [115]. The albumin-FITC also has a high molecular weight similar to the enzyme. A study concluded that this technology is capable of reliably delivering albumin-FITC across the BBB, as opposed to the only albumin which cannot cross the BBB alone [115]. However, there have been no investigations on whether the model drug or the MPS enzyme itself can function after crossing the BBB while bound to the PLGA nanoparticles and 7-amino acid glycopeptide complex. This therapy is currently in preclinical stages.

Bone-targeting ERT

The mechanism involves targeting hydroxyapatite, which is an inorganic molecule only found in hard bone. During bone reabsorption, drugs attached to hydroxyapatite may be released, supplying the drug directly to bone [116]. Molecules with repetitive glutamic acid sequences have been found to readily attach to hydroxyapatite [117]. For MPS IVA, attaching Glu6 (E6) onto the deficient enzyme GALNS targets bone more effectively than nonmodified GALNS [18]. Another modifier used is the sulfatase modifying factor 1 (SUMF1) with GALNS. SUMF1 gene catalyzes converting cysteine to formylglycine, which is directly involved in increasing sulfatase activity [118]. Sulfatases catalyze GAG hydrolysis. Thus, modifying the GALNS gene with both SUMF1 and E6 could target the bone and enhance GAG degradation in MPS IVA patients. Both adult and newborn MPS IVA mice treated with E6-SUMF1 GALNS showed a reduction of GAG storage in growth plates, but none reached complete clearance [18].

Improvements in skeletal dysplasia and other bone pathologies in MPS IVA mice have been limited with conventional ERT even during early initiation of treatment or even with a higher dose of 1000 U/g (4 mg/kg) [57, 119]. Therefore, another preclinical study on MPS IVA mice was conducted by using a modified protein of rhGALNS with hexaglutamate sequence (E6) to target bone [18]. After a single IV infusion of 1 mg/kg of rhGALNS-E6, MPS IVA mice had an increase in enzyme activity in bone and bone marrow for a prolonged time [18]. After 24 weekly IV infusions of 250 U/g with rhGALNS-E6, MPS IVA mice had a significant reduction of storage materials in heart valves, growth plates, and bone marrow, and more clearance was observed on MPS IVA newborn mice [18]. Thus, bone-targeting ERT provides more impact on bone pathology, compared with conventional ERT; however, further investigation of optimal dose, frequency, and the immune response is required.

Alternate administrations

One method penetrating the BBB is to administer the drug directly within the cranium or spinal cavity. Drugs in the CSF provided a longer half-life, compared with plasma due to minimal protein binding [91]. With the direct infusion, alterations to the drug or fusion proteins are not required as the infused drug breaks the BBB. However, this method may require an implanted device to deliver the drug. The

invasive nature of the administration may cause complications related with the device.

Intrathecal (IT)

IT ERT has been tested in clinical trials for MPS I, II, IIIA, and VI, but a limited amount of information on efficacy has been disclosed until now. Clinical trials investigating IT administrations on MPS II, IIIA, and VI have been discontinued due to the absence of significant clinical efficacy.

For MPS I, laronidase ERT via IT had a phase I clinical trial, which was discontinued due to slow enrollment in 2013 [13]. There has been no further report of this study.

A newer clinical trial and extension study administered 1.74 mg of laronidase via IT every 1–3 months in patients 6 years or older with cognitive decline present [120, 121].

Patients with MPS II received 10 mg of idursulfase via IT for 12 months [122]. The phase I/II study showed that CSF GAG levels were reduced by about 90% in both the 10 mg and 30 mg treatment groups after 6 months of IT idursulfase monthly plus an additional 0.5 mg/kg IV idursulfase weekly [123]. Results of idursulfase via IT for MPS II in phase II/III failed to meet endpoints evaluating General Conceptual Ability and Adaptive Behavior Composite score [124].

ERT for MPS IIIA administered via IT failed to slow cognitive decline in patients [125, 126]. Most patients had serious AEs related to the IT drug-delivery device that included catheter/port disconnections, migrated catheter, etc [126, 127]. IT ERT did not provide significant benefit on neurocognitive development.

IT administration does not need to remove equal amounts of CSF to maintain intracranial pressure, unlike ICV (see below). However, with IT administration utilizing an implanted catheter into the spinal cavity, complications occurred, including catheter displacement/kinking/leakage, device malfunction, and infection [91].

Thus, IT ERT has several obstacles to overcome before being considered as a viable treatment option.

Intracerebroventricular

Currently, two clinical trials with ICV are underway. One therapy for MPS IIIB was described above as rhNAGLU fused with IGF2. Another therapy for MPS II is under a phase I/II clinical trial with idursulfase beta via ICV administration [128].

In an MPS II murine model, idursulfase beta via ICV proved to significantly reduce and maintain HS levels in CSF and brain for 28 days, after a single injection of 30 µg [129]. The mice showed an improvement in memory/learning functions observed in open-field and fear-conditioning tests [129].

Another ICV ERT study on MPS IIID mice with recombinant human glucosamine (N-acetyl)-6-sulfatase (rhGNS) is underway. In MPS IIID neonatal mice, 5 µg of rhGNS was injected via ICV, and the enzyme activity in the brain increased to about threefold higher than carrier levels [130].

ICV administration requires invasive procedures. ICV administration, for example, may use an Ommaya reservoir implanted underneath the scalp to continuously infuse enzyme or neurosurgery to weekly infuse enzyme. The Ommaya reservoir may provide more comfort and allow a longer infusion time; however, malfunctions with the device such as meningitis, hemorrhage, and seizures may occur with either method [91]. Another consideration for the ICV route is maintaining the same intracranial pressure caused by CSF volume in the cranium. With the addition of any drug, the removal of equal amounts of CSF must occur, ensuring the intracranial pressure does not change too dramatically [91]. Other reports on safety and efficacy had been case studies which varied widely in procedure and variables measured [91]. Therefore, ICV ERT is considered a viable treatment option.

Discussion

Compared with HSCT, advantages of ERT are that ERT does not require a donor and can be conducted sooner than HSCT at any medical facility at any age or under most medical conditions [131, 132]. A combination of ERT and HSCT may stabilize pulmonary function in MPS I children, even with preexisting pathology [133, 134]. Since there was no evaluation of any other organ system using endurance testing, IQ/DQ testing, echocardiogram, or magnetic resonance imaging, a comprehensive assessment of combination therapy of ERT and HSCT remains unsolved.

Notably, prenatal lysosomal GAG storage appears in MPS patients and animal models. Human fetuses with MPS I, II, III, IVA, and VII already develop storage materials in chondrocytes and other major organs at 18–30 weeks gestation [57, 135–137]. Newborn mice with MPS I, II, IVA, or VII also have storage materials in chondrocytes [138, 139]. X-rays of the neonatal MPS IVA patient with sacral dimple have shown mild anterior beaking of vertebral bodies and round lumbar vertebral body, which may indicate early presence of skeletal dysplasia [140]. Skeletal abnormalities manifest the earliest clinical observations in MPS. Since the storage materials are already present in the early fetus, it remains unknown whether early introduction of ERT leads to complete clearance of storage materials in avascular cartilage and CNS.

Nevertheless, the benefits have increased with early detection and early treatment. Early detection depends on implementing MPS into the newborn screening. However, only a limited number of states in the United States and several countries are currently conducting newborn screening for MPS I [141].

Significant disadvantages of ERT includes the high-cost and life-long injections of the drug, which can deter some patients from receiving the weekly infusion due to financial or compliance reasons (Table 7). A typical infusion session is 4–5 h weekly, which disrupts the patient's daily activities [142]. Some types of MPS may require both systemic infusions via IV and direct infusions to the CNS, which may lead to a higher cost.

ERT often reduces total uGAG levels substantially; however, a continuous presence of HS and DS is observed in the urine despite long-term therapy, and no correlation with clinical improvement and reduction of uGAG is proved [143, 144]. Moreover, DS and HS in plasma or serum remained elevated in MPS I, II, and IVA ERT patients [41, 52, 144–147]. Thus, total uGAGs may not be the appropriate biomarker to evaluate therapeutic efficacy correlating with clinical improvement in brain and bone involvement, etc [52, 144, 148]. For circulation in the brain, lower levels of CSF GAGs build up correlate with attenuated MPS II patients, and higher levels of GAGs in the CSF have been shown in patients with cognitive involvement [149]. However, IT ERT provided substantial reduction of CSF GAGs, but recovery of cognitive function was limited. Therefore, it remains unclear that the reduction of CSF GAG (HS) correlates with the improvement of cognitive function [150].

CSF is produced primarily in the choroid plexuses of the ventricles of the brain at the physiological state [151]. It remains unknown about the origin of CSF GAG in patients with MPS although the majority of GAGs are coming from choroid plexus. GAGs may be produced in meningea, cerebral cortex, gray matter, or white matter and collected to arterial blood in the choroid plexuses. Reduction of CSF GAGs by ERT may only project the superficial anatomy of the brain nearest to CSF—meninges and choroid plexus. Therefore, it is critical to investigate the origin of GAGs in patients.

Route of administration and dosage are critical to penetrating the BBB because enough enzymes must reach the CNS. HIR-MAb/IDUA for MPS I has been indicated to significantly pass the BBB of a rhesus monkey but provided low enzyme levels in CSF [92]. Uptake of hTfR-MAb IDS for MPS II mice was about 1–2% ID/g in the brain and spinal cord from a 0.67 mg/kg IV infusion [152]. Although these new enzymes have been shown to penetrate the BBB, the infused enzyme alone may not be enough to provide an impact on cognitive function. More research is required on

Table 7 Approved ERT prices

Name	Manufacturer	Indication and US prevalence (per 10,000 newborns)	Route	Dose	WAC per year[a]
Aldurazyme (Laronidase)	Genzyme	MPS I 0.02–0.1	IV	0.58 mg/kg once per week	$218,000
Elaprase (Idursulfase)	Shire	MPS II 0.06–0.1 (Only male)	IV	0.5 mg/kg once per week	$340,000
Hunterase (Idursulfase beta)	Green Cross	MPS II 0.06–0.1 (Only male)	IV	0.5 mg/kg once per week	NA
Vimizim (Elosulfase alfa)	BioMarin	MPS IVA 0.03–0.05	IV	2 mg/kg once per week	$578,000
Naglazyme (Galsulfase)	BioMarin	MPS VI 0.017–0.04	IV	1 mg/kg once per week	$476,000
Mepsevii (Vestronidase alfa)	Ultragenyx Pharmaceutical	MPS VII 0.04	IV	4 mg/kg once per 2 weeks	$550,000

Prices from Simon-Kucher & Partners, FDA, PriceRx, NIH, and NORD

WAC wholesale acquisition cost, *NA* not available

[a]Price calculated from 25 kg patient

the effects of reducing CSF GAGs in patients with present cognitive impairment and what level the CSF GAGs at which age and which disease stage need to be reduced to stabilize, slow progression, or stop neuropathy. With a low percentage of the injected dose passing the BBB, the current dosage via IV may not be sufficient to improve cognitive function [99].

It is notable that an ERT of 300 mg administered via ICV every other week was approved for CLN2 disease, Batten disease, which is an LSD with severe cognitive impairment [153]. In a clinical trial with cerliponase alfa, the approved drug for Batten disease, patients had a smaller decrease in motor–language score than the historical controls, which demonstrates efficacy in the CNS [154]. The approval of cerliponase alfa may demonstrate that a high dose, such as 300 mg, is tolerated by the CNS, but it remains unclear whether treatment of MPS disease requires such a high dose or a different dose for CNS effect. Furthermore, the results for cerliponase alfa do not reverse CNS decline but slow the decline [154].

If the minimum effective dose for CNS improvement is 300 mg with direct infusion for a 30-kg patient like Batten disease or MPS IIIB, 500 mg/kg via IV is required for the patient since only 2% of the IV-injected dose is reaching the brain. Furthermore, three discontinued therapies administered via IT also had the doses ranging from 1.74 mg monthly to 45 mg biweekly, but all of which are far lower than 300 mg weekly, which may have been attributed to lack of therapeutic efficacy [14–17]. Since the clinical trials targeting CNS evaluate different MPS types, different routes of administration, different enzymes, and different disease stages, these confounding variables must be considered to make conclusions about the minimum effective dose for CNS and the optimal route of administration.

Immune responses of the drug must be monitored for neutralizing the enzyme activity, infusion-related reactions, and anaphylaxis events. Most data from animal models suggest high ADAs affecting efficacy, but there is little evidence of effect correlation between high titers and therapeutic efficacy in humans. Infusion-related reactions are usually resolved by either interruption of therapy, slowing rate of infusion, and/or administration of corticosteroids, antihistamines, and antipyretics [155, 156]. These infusion-related reactions usually occur during the first 3 months of starting ERT, so naïve patients should be monitored closely [155, 156]. All approved ERTs recommend discontinuing treatment if anaphylaxis occurs [157–161]. Pretreatment of antipyretics and/or antihistamines is often recommended by the FDA before administering the enzyme [158–161]. Ultimately, only a small portion of patients with ERT develop IgE antibodies and have anaphylaxis events to the ERT. Thus, infusion-related reactions can occur, but they are often manageable by slowing the infusion and/or administering appropriate medication. It would be worthy of monitoring ADA titers in serum and CSF to assess if they correlate with therapeutic efficacy.

Conclusion

ERTs for MPS have been developed and provide a better prognosis if initiated before clinical manifestations appear; however, ERT is often criticized for the high cost and inconvenient weekly infusions as well as limited impact on CNS, cardiovascular pathology, skeletal dysplasia, and pulmonary function. The future for ERT requires innovation to the enzyme, administration route, and/or dosage to reach targeted tissues where conventional ERT cannot impact.

Different strategies for resolving these issues are required without compromising the minimal immunogenic effects.

Acknowledgements This work was supported by grants from The Carol Ann Foundation, Angelo R. Cali & Mary V. Cali Family Foundation, Inc., The Vain and Harry Fish Foundation, Inc., The Bennett Foundation, Jacob Randall Foundation, Austrian and Japanese MPS societies, and Nemours Funds. This work was supported by the project for baby and infant in research of health and development to Adolescent and young adult from Japan Agency for Medical Research and development, AMED, under grant number JP18gk0110017. RWM and ST were supported by an Institutional Development Award (IDeA) from the National Institute of General Medical Sciences of National Institutes of Health (NIH) under grant number P30GM114736. The content of the article has not been influenced by the sponsors.

Author contributions HHC is the primary author of this article and has contributed to the concept, planning, data analysis, and reporting of the work described. KS is an expert in pharmacokinetics. He has 10 years of research experience in model mice for translational research and drug development. He has contributed to the editing, data analysis, and reporting of the work described. RWM has contributed to the concept and planning of the project, the draft of the manuscript, and reporting of the work described. HK has contributed to the concept and planning of the project, interpretation of GAG data, and reporting of the work described. SY has contributed to the concept and planning of the project, interpretation of GAG data, and reporting of the work described. YS has contributed to the concept and planning of the project, interpretation of clinical data, and reporting of the work described. TO has contributed to the concept and planning of the project, interpretation of clinical pictures, and GAG data, interpretation of published data and reporting of the work described. ST is a Principal Investigator for this project and has 30 years of clinical and research experience in Morquio A, publishing over 70 articles in this field. He has contributed to the concept, planning, interpretation of published data, and reporting of the work described.

Compliance with ethical standards

Conflict of interest HHC, KS, RWM, HK, SY, YS, TO, and ST contributed to the Review Article and had no conflict of interest with any other party. All authors declare that they have no conflict of interests.

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