

# Diagnosis and Emerging Treatment Strategies for Mucopolysaccharidosis VII (Sly Syndrome)

Fabiano de Oliveira Poswar<sup>1-4</sup>, Johanna Henriques Nehm<sup>1</sup>, Francyne Kubaski<sup>5</sup>, Edina Poletto<sup>6</sup>, Roberto Giugliani<sup>1-4,7-9</sup>

<sup>1</sup>Clinical Research Group in Medical Genetics, Clinical Research Center, Hospital de Clínicas de Porto Alegre, Porto Alegre, RS, Brazil; <sup>2</sup>Medical Genetics Service, Hospital de Clínicas de Porto Alegre, Porto Alegre, RS, Brazil; <sup>3</sup>Postgraduate Program in Genetics and Molecular Biology, UFRGS, Porto Alegre, RS, Brazil; <sup>4</sup>DR Brasil Research Group, HCPA, Porto Alegre, RS, Brazil; <sup>5</sup>Greenwood Genetic Center, Biochemical Genetics Laboratory, Greenwood, SC, USA; <sup>6</sup>Department of Pediatrics, Stanford University School of Medicine, Stanford, CA, USA; <sup>7</sup>Department of Genetics, UFRGS, Porto Alegre, RS, Brazil; <sup>8</sup>DASA Genômica, São Paulo, SP, Brazil; <sup>9</sup>Casa dos Raros, Porto Alegre, RS, Brazil

Correspondence: Roberto Giugliani, Medical Genetics Service- HCPA / Dep Genet UFRGS, 2350 Ramiro Barcelos, Porto Alegre, RS, 90035-903, Brazil, Tel +55 51 3359 6338, Email rgiugliani@hcpa.edu.br

**Abstract:** Mucopolysaccharidosis VII (MPS VII, Sly syndrome) is an ultra-rare lysosomal disease caused by a deficiency of the enzyme  $\beta$ -glucuronidase (GUS). The diagnosis is suspected based on a range of symptoms that are common to many other MPS types, and it is confirmed through biochemical and molecular studies. Besides supportive treatment, current and emerging treatments include enzyme replacement therapy, hematopoietic stem cell transplantation, and gene therapy. This review summarizes the clinical manifestations, diagnosis, and emerging treatments for MPS VII.

**Keywords:** lysosomal disorders, mucopolysaccharidosis type VII, Sly syndrome, enzyme replacement therapy, hematopoietic stem cell transplantation, gene therapy

## Introduction

Mucopolysaccharidoses (MPSs) form a heterogeneous group of disorders caused by the deficiency of one of the enzymes involved in the breakdown of glycosaminoglycans (GAGs), which takes place in the lysosome. There were 11 enzyme deficiencies classically recognized,<sup>1</sup> but recently arylsulfatase K deficiency was described and added to this group.<sup>2</sup> Although the disease seems to originate from abnormal storage of GAGs, it is now accepted that the primary GAGs storage triggers a pathogenic cascade, with many other factors involved, including inflammation.<sup>3</sup>

Patients with MPS may present severe manifestations that could include non-immune hydrops fetalis (NIHF)<sup>4</sup> and/or early neurodegeneration, or have a more attenuated phenotype that could be marked by corneal clouding and mild bone and joint abnormalities.<sup>5</sup> This heterogeneity is clear not only across the different MPS types but also within the same type, with different variants and levels of residual enzyme activity. Several contributions aiming to establish genotype–phenotype correlations were already published.<sup>6</sup>

Mucopolysaccharidosis type VII (MPS VII, Sly syndrome) was first described in 1973 when the deficiency of the enzyme  $\beta$ -glucuronidase (GUS, EC 3.2.1.31) was found in a patient with MPS-like clinical and radiological findings.<sup>7</sup> Thereafter, the *GUSB* gene that codifies beta-glucuronidase was cloned and mapped.

Soon it was recognized that MPS VII is an ultra-rare condition, with an estimated incidence of less than one case per 1,000,000 individuals, being responsible for less than 2% of MPS cases in most series.<sup>8,9</sup>

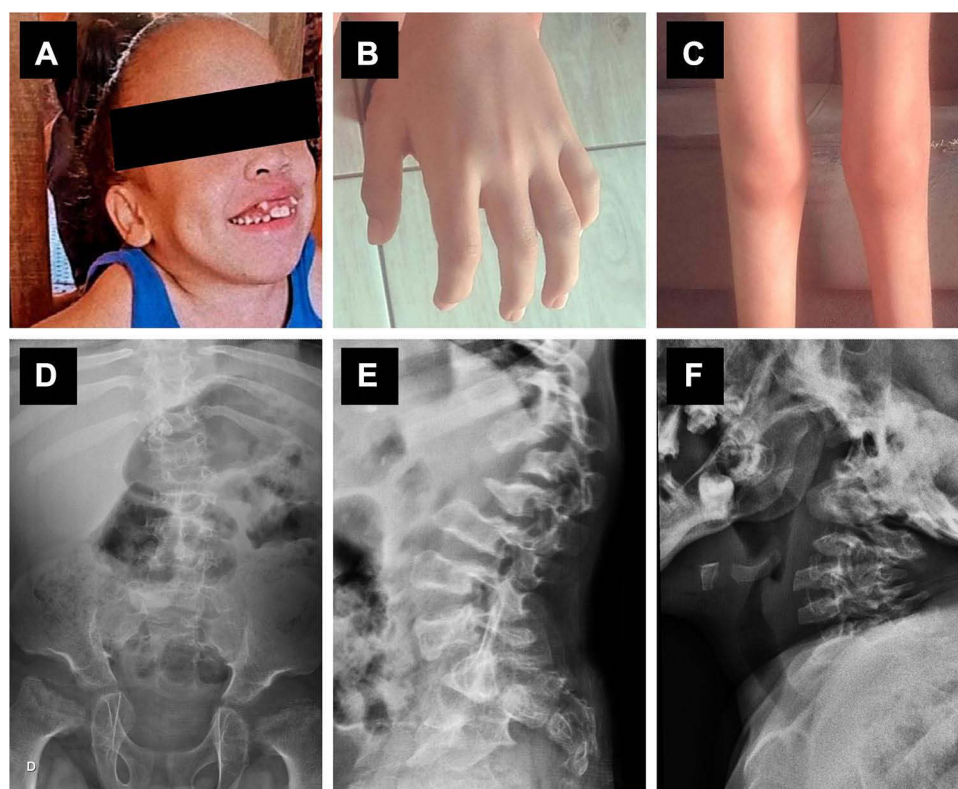
This paper will review the clinical manifestations of MPS VII, the approach to diagnosis, the current treatment measures, and the emerging therapeutic strategies.

## Clinical Manifestations

Patients with MPS VII have a wide range of manifestations, including cognitive impairment, hepatosplenomegaly, coarse facial features, cardiac valve disease, recurrent upper respiratory infections, short stature and bone dysplasia (Figure 1). These signs and symptoms are very similar to those described in other types of MPS, particularly the MPS types I and II.<sup>10</sup> As in other MPS types, the age of onset of the signs and symptoms may be different according to the disease severity, and in the milder end of the severity spectrum, preservation of cognition may occur.

A distinctive feature of MPS VII, however, is the high proportion of patients that present with severe antenatal disease including NIHF. Complications related to NIHF are also a major cause of death for patients with MPS VII, and about half of the patients do not survive beyond 1 year of life.<sup>11</sup> Since the first description of NIHF as a form of presentation in 1982, it has been proposed to include MPS VII in the diagnostic workup for NIHF.<sup>12</sup> It is now recognized that MPS VII is among the most common lysosomal disorders identified in this context.<sup>4,13</sup> Besides, more than 10 cases of prenatal diagnosis of MPS VII due to suggestive features were reported.<sup>14</sup> However, as this investigation is not always performed, some patients with MPS VII die from NIHF without being properly diagnosed, and a lysosomal disorder is only considered after familial recurrence.<sup>15</sup>

The circumstance in which the diagnosis is established is associated with clinical outcomes. Patients who are diagnosed prenatally, even when pregnancy is not terminated, usually have a very limited survival. Most of those patients die at late pregnancy or soon after birth due to heart, kidney, or respiratory failure.<sup>11,14,15</sup> In the cases diagnosed postnatally, MPS VII remains an early-onset and severe condition with the median disease onset being the first day of life, and the median survival being 42 months.<sup>14</sup> However, the clinical course is variable, and it is not entirely predicted by the presence of NIHF by itself. For instance, in a case series including 23 patients with a history of NIHF, 13 survived the infancy period with a mild to intermediate phenotype.<sup>11</sup>



**Figure 1** Clinical manifestations of MPS VII. Clinical photographs show coarse facial features, with a short neck and abnormal dentition (A), as well as joint contractures with claw hands (B), and genu valgum (C). Radiographic signs of dysostosis multiplex include broad ribs, hip dysplasia and scoliosis (D); thoracolumbar gibbus (E); odontoid dysplasia (F). Informed consent was obtained for the publication of patient images.

**Table 1** MPS VII Manifestations

Clinical Manifestation	Age of Onset <sup>7,12,23,38</sup>	Prevalence in MPS VII Patients <sup>11,14,23,38</sup>	Supportive Treatment
Non-immune hydrops fetalis	Antenatal	25–50%	Standard neonatal resuscitation
Radiological signs of dysostosis multiplex	0–2 months	>75%	NA
Coarse facial features	0 months–5 years	>75%	NA
Hepatomegaly/splenomegaly	0–2 months	>75%	NA
Macrocephaly	2–5 months	>75%	NA
Gibbus/spinal deformities	2–5 months	50–75%	Spine surgery <sup>11</sup>
Umbilical and inguinal hernias	5 months	50–75%	Hernia repair <sup>11</sup>
Corneal clouding	5 months	50–75%	Keratoplasty <sup>101</sup>
Developmental delay/intellectual disability	6 months–2 years	>75%	Learning support, speech and language therapists <sup>23</sup>
Thick hair/eyebrows	6 months–10 years	50–75%	NA
Hip dysplasia	9 months–4 years	50–75%	Pain medications; pelvic plaster; hip replacement <sup>11</sup>
Hydrocephalus	9 months	<10%	Ventriculoperitoneal shunting <sup>102</sup>
Recurrent upper airway infections	1 year	25–75%	Antibiotics, removal of adenoids and tonsils, ventilation tubes <sup>11,23</sup>
Decreased pulmonary function and sleep disturbance	1–15 years	50–75%	Tracheotomy, oxygen supplementation, non-invasive ventilation <sup>11,38</sup>
Dental anomalies	1–10 years	50–75%	Dental treatment, including orthodontic treatments <sup>23</sup>
Short stature	1.5 years	>75%	NA
Spinal cord compression	1.5–14 years	25–50%	Surgical decompression or spinal fusion <sup>11</sup>
Hearing impairment	2.5 years	10–25%	Ventilation tubes, hearing aids <sup>23</sup>
Challenging behavior	2–10 years	50–75%	Behavior management <sup>23</sup>
Cardiac valve disease and cardiomyopathies	5 years	25–50%	Standard medications for heart failure; valve replacement <sup>99</sup>
Joint stiffness or pain	6–25 years	>75%	Physical therapy; non-steroidal anti-inflammatory drugs <sup>11</sup>

**Note:** Prevalence of non-immune hydrops fetalis as a clinical manifestation may be underestimated, as many cases are not investigated for MPS VII.

**Abbreviation:** NA, not applicable/available.

The knowledge about the natural history and the range of clinical manifestations associated with MPS VII is important to recognize high-risk groups of patients for selective screening.<sup>10</sup> Table 1 summarizes the clinical manifestations of MPS VII, their age of onset, and frequencies.

## Diagnosis

### Biochemical diagnosis

The biochemical diagnosis of MPS VII consists of the quantification of the activity of GUS, which is required for the stepwise degradation of glucuronic acid-containing GAGs: chondroitin sulfate (CS), dermatan sulfate (DS), and heparan sulfate (HS).<sup>1,7,11,16,17</sup>

The enzyme deficiency can be demonstrated in serum, leukocytes, cultured fibroblasts, or dried blood spots (DBS) using fluorimetry with 4-methylumbelliferyl (4-MU) derived substrate,<sup>11,17,18</sup> and in DBS using liquid chromatography tandem mass spectrometry.<sup>19,20</sup>

The enzyme assay is usually performed when clinical suspicion is raised in symptomatic patients, or in asymptomatic individuals who are considered at risk due to family history. In the prenatal period, the measurement of enzyme activity can be performed in chorionic villus,<sup>21–23</sup> cultured amniocytes,<sup>15</sup> or leukocytes from blood from the umbilical cord.<sup>15</sup>

GAG quantification can aid biochemical diagnosis. Several methods can be employed for GAG analysis, the most used methods are dimethylmethylene blue (DMMB),<sup>24</sup> electrophoresis,<sup>25</sup> and quantification by liquid chromatography–tandem mass spectrometry (LC-MS/MS).<sup>25</sup> LC-MS/MS offers several advantages compared to the conventional

colorimetric methods: precise and accurate quantification, discrimination of GAG subclasses or GAG-derived oligosaccharides, and it can be employed in a variety of sample types (urine, plasma/serum, DBS, cerebrospinal fluid, cells, tissues, synovial fluid).<sup>25–31</sup> GAG quantification can also be performed in the supernatant of amniotic fluid and it is very helpful to support the prenatal investigation.<sup>32</sup> Additionally, it can be used for therapeutic monitoring.<sup>25–31</sup>

Saville and colleagues reported a novel method for the quantification of disease-specific signatures from GAGs in which urine samples can be derivatized, allowing the identification of GAG fragments unique to specific MPS subtypes; this allows the identification of MPS VII by the elevation of the nonreducing end fragment UA-HN-UA (1S) [uronic acid–hexosamine–uronic acid] which is exclusively elevated in the urine of MPS VII patients.<sup>30</sup>

As pseudodeficiency of beta-glucuronidase has been reported, GAG analysis combined with molecular analysis can discriminate true MPS VII-positive results from reduced in vitro enzyme activity due to pseudodeficiency.<sup>11,33–35</sup>

## Molecular Diagnosis

Molecular genetics testing is usually recommended for the confirmation of the biochemical diagnosis. Moreover, it allows identification of carriers, appropriate genetic counseling for families, and prenatal genetic testing for additional pregnancies.

The enzyme GUS is encoded by the 20 kb-long glucuronidase beta gene (*GUSB*, OMIM# 253220), located in the long arm of chromosome 7 (7q11.21–7q11.22). It contains 12 exons that encode for a 651-amino acid precursor and a mature 629-residue protein and displays significant genetic heterogeneity.<sup>34</sup> Multiple pseudogenes or fragments containing *GUSB* sequences were identified in different chromosomes across the human genome, hampering the initial sequencing of the gene.<sup>36</sup> A few pseudodeficiency alleles have also been described.<sup>35,37</sup>

There are currently 80 disease-causing variants described in the *GUSB* gene; most of them (74%) are missense variants, others are nonsense (11%), splicing (5%), or small deletions and indel variants (7%) (HGMD Professional, accessed on 06/14/2022). Some cohorts of MPS VII patients have more heterogeneous genotypes, with novel variants constantly being described and frequent compound heterozygosity observed.<sup>34,38</sup> Because it is an ultra-rare disease, only dozens of patients were reported worldwide, with the higher incidence in the region of British Columbia and in The Netherlands, with a prevalence of 0.29 and 0.24 cases per 100,000 live births, respectively.<sup>8</sup>

The most common MPS VII-causing variant is p.Leu176Phe, found in patients from different cohorts worldwide.<sup>34,38,39</sup> In Brazil, for example, this variant accounts for 96% of the alleles identified in MPS VII patients.<sup>39</sup> Due to its presence in homozygosis in attenuated MPS VII patients and to the prediction from in vitro and in silico studies, this variant was originally associated with the attenuated phenotype of the disease.<sup>34</sup> However, more recent reports of p.Leu176Phe homozygotes showed patients with variable clinical manifestations, including in the severe spectrum,<sup>11,39</sup> suggesting the genotype–phenotype correlation is not as straightforward as previously thought and other factors might be influencing it. The other most frequent pathogenic variants are also exonic point mutations – p.Arg357Ter, p.Pro408Ser, p.Pro415Leu, and p.Ala619Val.<sup>34</sup>

The attenuated phenotype is traditionally thought to be associated with residual enzyme activity, as this is generally true for other lysosomal disorders. However, some MPS VII patients have attenuated phenotypes despite the very low GUS activity,<sup>39,40</sup> indicating that the residual activity alone is not predictive of the clinical course.

## Treatment

### Enzyme Replacement Therapy

Enzyme replacement therapy (ERT) is a treatment available for several LSDs. It was initially approved in 1990 for Gaucher disease, with great results. From 2003 onwards, it began to be used for mucopolysaccharidoses, with positive results across many disease manifestations. Vestronidase alfa is the first ERT developed to treat patients with mucopolysaccharidosis VII.<sup>41</sup> It is a formulation of recombinant human GUS (rhGUS) that has previously been successfully treated in an animal model.<sup>42</sup> It is produced using a genetically modified Chinese hamster ovary cell line, similar to laronidase, the enzyme used to treat MPS I. However, vestronidase alfa has a longer enzyme half-life after absorption in fibroblasts, when compared to laronidase (40 days vs 3 to 4 days, respectively).<sup>43</sup> Through mannose-6 phosphate (M6P)

residues present in oligosaccharide chains, the enzyme can bind to M6P receptors on the surface of cells. Subsequently, vestronidase alfa is internalized into cellular lysosomes, and it degrades GAGs accumulated in affected tissues.<sup>44</sup>

Due to the rarity and clinical variability of mucopolysaccharidosis VII, the development of a specific treatment for this disease was considered very challenging, making animal models that present a disease similar to humans of paramount importance. Mice with MPS VII provide a good model for LSDs, as the effectiveness of treatments can be phenotypically confirmed. Animal models of dogs with MPS VII have also been reported.<sup>45</sup> Preclinical studies with the MPS VII murine model using rhGUS purified with sodium metaperiodate and sodium borohydride to inactivate the M6P recognition markers revealed reduced GAG accumulation in lysosomes, improvements in various soft and connective tissues such as bone, improved animal survival, and decreased accumulation of GAGs in the brain.<sup>46</sup> Other preclinical studies in adult mice tagged a short peptide consisting of fatty acids to rhGUS showed that 4 mg/kg intravenously reduced neuronal and glial storage in the brain after 12 weeks of treatment.<sup>47</sup> In neonatal dogs with MPSVII, ERT demonstrated resolved mitral valve regurgitation.<sup>48</sup>

Three clinical trials were conducted to assess the efficacy and safety of vestronidase alfa (see Table 2). In an open-label Phase I/II clinical trial to determine the dose, 4 mg/kg intravenous vestronidase alfa was administered every 2 weeks (QOW) without any significant safety concerns (ClinicalTrials.gov: NCT02418455). A Phase II clinical trial in subjects <5 years of age was performed to determine additional evidence for the long-term safety and efficacy of vestronidase alfa. Lastly, a placebo-controlled Phase III clinical trial evaluated the use of recombinant human beta-glucuronidase (alphavestronidase) in 12 patients with MPS VII.<sup>49</sup> The sample was composed of 8 females and 4 males, with an age range of 8–25 years, the majority of them being white (75%) and of Hispanic or Latino ethnicity (50%). In order to account for a heterogeneous sample, a novel blind start study design with a variable placebo run-in period was used. While urinary GAG (uGAG) excretion was the primary endpoint, clinical response was also assessed by using a multi-domain responder index (MDRI). The MDRI consists of the following clinical domains: 6-minute walk test, forced vital capacity, shoulder flexion, visual acuity, and Bruininks–Oseretsky Test of Motor Proficiency. After 24 weeks of treatment, uGAG excretion levels were significantly reduced in all subjects. Furthermore, 10 in 12 patients had

**Table 2** Clinical Trials for MPS VII

Study Identification	Type	Phase	Drug	Clinical Trials
<b>UX003-CL201</b>	Interventional	Phase I/II	UX003 (Vestronidase alfa)	NCT01856218
<b>UX003-CL301</b>	Interventional	Phase III	UX003 (Vestronidase alfa)	NCT02230566
<b>UX003-CL202</b>	Interventional	Phase III	UX003 (Vestronidase alfa)	NCT02432144
<b>UX003-CL203</b>	Interventional	Phase II	UX003 (Vestronidase alfa)	NCT02418455
<b>UX003-CL401</b>	Observational prospective	NA	NA	
<b>I3-606</b>	Interventional	NA	UX003 (Vestronidase alfa)	NCT02097251
<b>BSLY-06-2018</b>	Observational prospective	NA	NA	NCT02298699
<b>UX003-EAP</b>	Interventional		UX003 (Vestronidase alfa)	NCT03775174
<b>U54NS065768</b>	Observational prospective	NA	NA	NCT01870375
<b>20-31520</b>	Interventional	Phase I	Aldurazyme (laronidase), Elaprase (idursulfase), Vimizim (elosulfase alfa), Naglazyme (galsulfase), Mepsevii (vestronidase alfa-vjbk), Lumizyme (alglucosidase alfa), Kanuma (sebelipase alfa)	NCT04532047
<b>MT2013-31</b>	Interventional	Phase II	Biological: Stem Cell Transplantation Drug: IMD Preparative Regimen (Anti-thymocyte Globulin (ATG), Fludarabine, Busulfan)	NCT02171104
<b>R01HD073292</b>	Observational prospective	NA	NA	NCT05368038
<b>MT2008-02</b>	Interventional	Phase II	Procedure: Stem Cell Transplantation Drugs: Cyclophosphamide, Campath-1H Drug: Busulfan	NCT00668564
<b>2009LS088/MT2009-19</b>	Interventional	Phase II	Procedure: Allogeneic stem cell transplantation Drugs: Campath-1H, Cyclophosphamide, Busulfan, Cyclosporine A, Mycophenolate Mofetil	NCT01043640



an improvement in at least one MDRI domain. In all three studies, vestronidase alfa was administered with antihistamine premedication, infusion rate titration, and careful patient monitoring, so no significant safety concerns were identified.<sup>50</sup>

On November 15, 2017, after nearly two decades of success with studies in animal models and other mucopolysaccharidoses, vestronidase alfa was finally approved for children and adults with MPS VII by the FDA in the United States.<sup>39</sup> As of 2018, vestronidase alfa was also authorized in the European Union (EU)/European Economic Area (EEA), UK, Brazil, Chile, and Mexico.<sup>51,52</sup> For the treatment of mucopolysaccharidosis VII, 4mg/kg of vestronidase alfa is given as a slow intravenous (IV) infusion once every 2 weeks. An antihistamine with or without a sedative action, with or without an antipyretic drug, should be administered 30–60 minutes before the infusion to reduce the risk of hypersensitivity.<sup>53</sup>

Although ERT treatment has shown efficacy, improving survival and quality of life of patients with MPS VII, treatment can be limited mainly because it does not modify the sequelae of the disease that are present until the time of treatment. In addition, postnatally applied vestronidase alfa does not cross the blood–brain barrier. Many patients can produce anti-enzyme antibodies and need immunomodulation to tolerate treatment.<sup>54</sup>

A study with ERT in utero in mice with MPS VII was performed, and 20mg/kg were administered to fetuses in the litter at embryonic day 14.5 by intrahepatic injection, while control mice received injections of vehicle or phosphate-buffered saline.<sup>54</sup> ERT in utero prevented the development of anti-enzyme antibodies, demonstrated an improvement in the survival of the animals, penetrated the brain microglia decreasing inflammation, and improved neurological tests such as grip strength, compared to mice treated only postnatally.<sup>55</sup> In utero therapy for MPS VII and other LSDs is being investigated through a Phase I clinical trial that started in 2021 in order to determine the maternal and fetal safety and the feasibility of in utero fetal enzyme replacement therapy in fetuses (Clinical Trials.gov: NCT04532047).

The prospect of a second generation of ERT with the use of brain penetrating enzymes, already approved in Japan for MPS II<sup>56</sup> and in development for MPS I, may be interesting for MPS VII also due to the high proportion of patients who present central nervous system (CNS) involvement.

## Hematopoietic Stem Cell Transplantation

Hematopoietic stem cell transplantation (HSCT) aims to correct the clinical manifestations of the disease by providing an active enzyme from the transplanted cells that can lead to substrate reduction.<sup>57</sup> Because of its incidence, there are not that many published cases of HSCT performed in MPS VII patients (n=9). Yamada and colleagues reported a case of a patient whose diagnosis was performed at 1 month of age, but only received an allogeneic bone marrow transplantation (BMT) when she was 12 years of age (already presenting neurological impairment, skeletal deformities, and wheelchair bound). Ten months post-transplant, the patient presented almost normal GUS levels and a decrease in uGAG excretion, as well as improvement in the clinical course, and shortness of breath in which she was able to walk, ride a bicycle, and take a bath alone. As expected, because of the age at transplant, her neurological impairment was not reversed.<sup>58</sup>

Montaño and colleagues reported the results of HSCT/BMT in five MPS VII patients. Two out of five patients had a positive outcome; the fifth patient had a BMT at 7 months of age, and the patient did not have any clinical manifestations at 15 months of age reaching normal development milestones (started walking at 1 year of age) highlighting the impact of early treatment. Nonetheless, the patient still has some cardiomyopathy with moderate atrial enlargement and a prominent forehead. The fourth patient underwent BMT at 3 years of age; 12 years post-transplant, the patient shows moderate clinical symptoms suggesting that the BMT might have somewhat slowed down disease progression. However, at the last exam, the patient still presents clinical symptoms, skeletal deformities, neurological impairment, and restrictive and obstructive respiratory disease. The first patient had a BMT at 2 years of age, which failed, and another BMT at 4 years of age. There is no long-term follow-up data in this case. The second patient underwent BMT at 7 years of age and died from transplant-related complications. The third patient had a very severe phenotype, there are no data reporting the age at the transplant, and the patient died years after the procedure.<sup>11</sup>

Sisinni and colleagues reported a 2-year-old MPS VII patient with a mild phenotype that underwent an allogeneic HSCT. The patient was submitted to HSCT twice due to the rejection of the graft in the first transplant. After

a myeloablative regimen was employed, there was engraftment after the second transplant with matched unrelated cord blood. Six years post-transplant, the patient showed normal GUS activity, reduction in total GAG levels (but still higher than age-matched controls), normal motor function, improvement of coarse facial features, resolution of organomegaly, and stabilization of skeletal deformities. Since the patient had a moderate phenotype, no scoliosis or neurological impairment was present pre- or post-transplantation.<sup>57</sup>

Another patient was treated by HSCT with unrelated human leukocyte antigen (HLA)-matched cord blood at 14 months of age. Besides the conditioning regimen employed, the patient had several infections: rotavirus gut, *Staphylococcus aureus*, cytomegalovirus reactivation; and graft-versus-host disease (GVHD) grade III that resolved, and the patient achieved full chimerism. The patient improved post-transplant and started walking at 20 months of age. However, the patient developed chronic pulmonary insufficiency in his second year of life and died at 25 months of age.<sup>59</sup>

Dubot and colleagues have reported a case in which the patient was diagnosed at 2 weeks of age, started ERT at 4 months of age, and received an HSCT at 13 months of age. The patient had developed severe skin and gut-GVHD in which ERT was stopped 6 months post-transplantation. At 4 years of age, the patient has normal psychomotor development, stabilized growth curve, and no organomegaly. This report highlights the need for an early diagnosis followed by early treatment.<sup>60</sup> Despite transplant-related complications, as long as the transplant is performed before the development of irreversible damage (mainly neurological and skeletal) HSCT can be considered a treatment option for MPS VII. For that purpose, it is also required that appropriate conditioning regimen is used and the patient reaches full engraftment. The outcome can be improved in cases where HSCT is combined with other therapeutic approaches such as ERT and gene therapy because HSCT has limited benefit in tissues such as bone, cartilage, eye, and the CNS considering the time of engraftment.<sup>11,60</sup>

## Gene Therapy and Genome Editing

Gene therapy uses recombinant nucleic acids to modify genetic sequences for therapeutic purposes. It can be done in vivo – when the product is administered directly to the patient – or ex vivo – when cells are modified in vitro and then transferred to the patient. MPS VII is a good candidate for gene therapy since a) it is a monogenic disorder, b) the deficient enzyme is soluble and can transit from an enzyme-producing cell to an enzyme-deficient cell, and c) restoring low levels of enzyme presumably is sufficient to lessen disease burden.

The availability of naturally occurring MPS VII animal models<sup>61–63</sup> propelled the development of many pre-clinical gene therapy studies in the 2000s. The MPS VII dog model, particularly, was extremely useful to evaluate the long-term efficacy of gene therapy, with some animals being followed up to 11 years post-treatment.<sup>64,65</sup> Most of the research done for MPSs used in vivo administration of viral vectors, due to their high efficiency in transducing cells and delivering the *GUSB* cDNA.

MPS VII mice and dogs treated intravenously with vectors based on lentivirus,<sup>66,67</sup> adeno-associated virus,<sup>68</sup> or retrovirus<sup>69,70</sup> showed increased enzyme activity and reduced GAG storage in visceral tissues, including hard-to-treat cardiovascular tissues, improving heart function.<sup>65,69–71</sup> Some improvements in the brain tissue as well as in behavior tests were reported in mice treated from birth<sup>66</sup> and in mice with the attenuated phenotype.<sup>72</sup> The skeletal disease was partially ameliorated in both animal models, resulting in a decrease in bone mineral volume, surface density, and thickness.<sup>66,72–76</sup> However, the treatment could not prevent lumbar spine disease,<sup>77</sup> and cartilaginous tissues were not much responsive to either vector. Although the therapy was administered systemically, uGAG levels were not reduced with gene therapy.<sup>67,73</sup> Other strategies such as plasmid vector<sup>78</sup> or ex vivo gene therapy of hematopoietic stem cells<sup>79</sup> were also tested in MPS VII mice with, however, low therapeutic efficacy.

Systemic administrations of viral vectors rose concern about the potential insertional mutagenesis these vectors can cause, as demonstrated by the high incidence of hepatocellular carcinomas developed in MPS VII-treated mice.<sup>80,81</sup> Thus, in situ gene therapy was pursued, as local injections require reduced viral titers and provoke fewer immunogenic responses.<sup>82</sup> Intracranial and intrathecal administrations of *GUSB*-expressing viral vectors showed reversion of the phenotype in the tissue, with increased enzyme activity and correction of storage lesions.<sup>67,83–86</sup> Treated mice also improved performance in behavioral studies<sup>87,88</sup> and had longer lifespans, with visceral tissues being corrected by

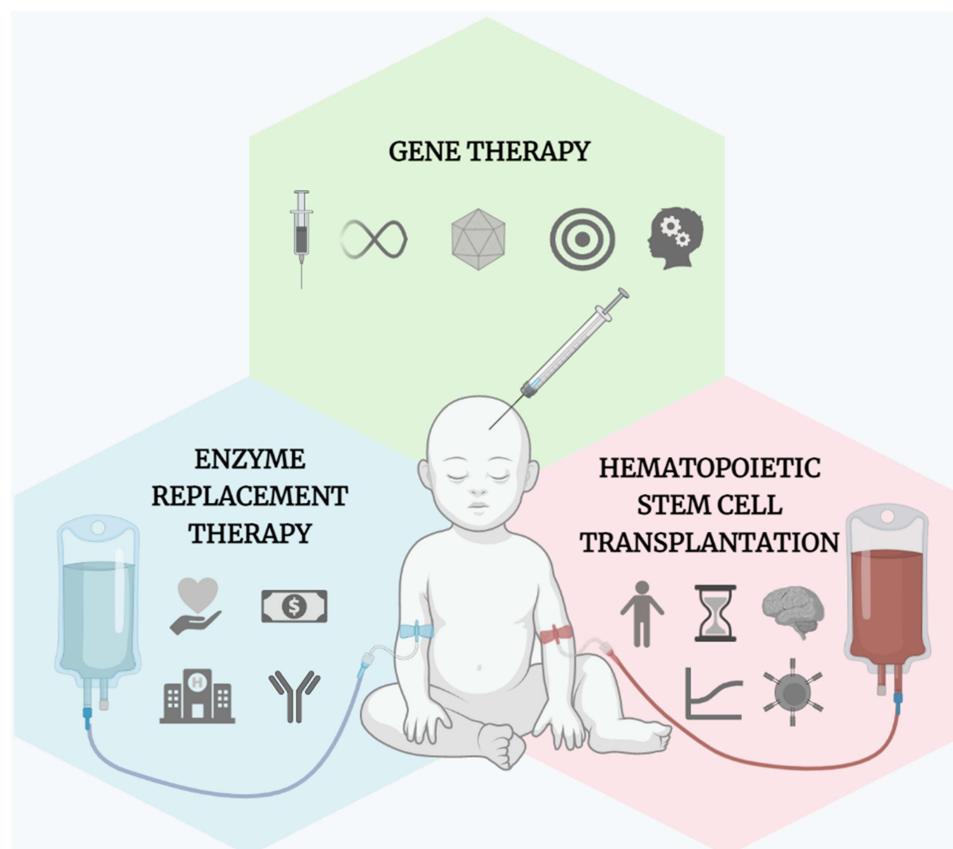
drainage of the vector to the bloodstream.<sup>85</sup> Interestingly, intravitreal administration also led to some biochemical correction in brain regions through diffusion and trans-synaptic transfer.<sup>89</sup>

Collective data with both mouse and large animal models pointed to in situ administration of viral vectors as the most efficient strategy so far to target the CNS. By that route of administration, normal or even supraphysiological levels of the enzyme can be achieved in the brain,<sup>90,91</sup> while intravenous injections failed. However, new strategies should address skeletal disease, which is one of the major disease burdens faced by patients.

Meanwhile, new gene therapy techniques – like genome editing – hold great promise for mucopolysaccharidoses.<sup>92</sup> Clinical trials for MPS I and MPS II already took place, while different approaches have been tested in the pre-clinical setting for these diseases, such as ex vivo,<sup>93</sup> and intravenous<sup>94,95</sup> or nasal<sup>96</sup> delivery of CRISPR-encoding plasmids. There are no complete studies targeting MPS VII with genome editing, though a couple of reports suggest this technique may be beneficial for the eye manifestations of the disease.<sup>97</sup> A comparison between ERT, HSCT, and gene therapy as therapeutic approaches for MPS VII is provided in Figure 2.

## Supportive Treatment

Despite advances in the development of specific therapies, patients with MPS VII remain with several health issues that require multidisciplinary care. These include not only sequelae already established before starting the therapy but also late complications that may eventually not be prevented by ERT, HSCT, or gene therapy. Adequate surveillance of the patients will ensure that disease complications are detected in the early stages and allow for better outcomes of



**Figure 2** Therapeutic approaches for MPS VII. Enzyme replacement therapy leads to significant improvement in patient's quality of life, with disease correction in many visceral tissues; however, it is costly, requires the support of health centers, and there is the possibility of immune reactions. Hematopoietic stem cell transplantation, on the other hand, is effective in the brain, though it must be performed early in life, it takes time for cells to fully engraft and be effective, a matching donor is necessary, and there is always a life-threatening risk of graft rejection or graft-versus-host disease. Finally, gene therapy should be a once-in-a-lifetime treatment (or a few times throughout the lifespan of the patient), able to target the central nervous system specifically and improve cognition significantly, although it can be a very invasive procedure with associated risks inherent to viral vectors.



supportive interventions. Patients may benefit from regular clinical consultations every 6 months, with laboratory, imaging, and functional tests done annually or as indicated.<sup>98</sup>

Developmental delay and neurological regression are very common in MPS VII.<sup>11</sup> A standard test for developmental quotient from a developmental specialist may be useful for monitoring the disease progression and guiding learning support. Neurological examination, brain and spine MRI, and nerve conduction velocities may also identify the presence of cord compression, hydrocephalus and carpal tunnel syndrome. Surgical interventions may be needed in those cases.<sup>23</sup>

Clinical examination may detect the presence and progression of joint contractures, scoliosis, genu valgum and other osteoarticular abnormalities. A radiological examination may clarify the presence of complications including hip dysplasia, and a referral to an orthopedic surgeon will be needed. Interventions applied in this context may include the use of nonsteroidal anti-inflammatory drugs, physical therapy, orthosis, and surgical procedures.<sup>11,23</sup>

Echocardiogram, pulmonary function tests and endurance tests, including 6-minute-walk test, should be performed to detect and monitor cardiopulmonary involvement. When exertional intolerance is present, NT-pro-BNP may be helpful to distinguish a cardiac cause from pulmonary and musculoskeletal involvement.<sup>99</sup> In advanced cases, heart failure may be managed by standard guidelines, and valve replacement should be considered.<sup>99</sup> A severe respiratory disease, on the other hand, may require oxygen therapy or the use of non-invasive ventilation.<sup>38</sup>

Regular surveillance for audiological, ophthalmological and dental manifestations are also required. When indicated, patients may benefit from different procedures including ear tube placement, hearing aids, keratoplasty and orthodontic treatment.<sup>23</sup>

While surgical procedures may be necessary for many of the MPS complications, it is important to emphasize that special caution is needed, since patients with MPS VII are at high anesthetic risk, due to difficult airway management, respiratory complications, and, more rarely, cardiac complications.<sup>100</sup> A summary of supportive treatments is presented in Table 1.

## Conclusion and Prospects

Along the almost 50 years after its initial report, much progress has been accomplished regarding the understanding and management of MPS VII. Its perinatal presentation with NIHF, observed in a large percentage of cases, is now well recognized, and screening for MPS VII in these patients became a common practice. Despite being an ultrarare disease and one of the less frequent MPSs, intensive pre-clinical and clinical research led to the development of specific enzyme replacement therapy. The fact that the rhGUS produced for MPS VII treatment (vestronidase alfa) has a longer half-life compared to other ERTs enables its administration every 2 weeks, a convenient advantage compared to the ERTs for the other treatable MPSs. The prospect of prenatal ERT is particularly interesting for this type of MPS, considering the high proportion of NIHF in affected patients. A new generation of ERT with brain penetrating enzymes may be interesting for this condition, considering the high proportion of patients who present CNS involvement. Still considering the CNS manifestations, HSCT seems to be a therapeutic alternative, but the risks related to this procedure should be weighted with the potential benefits, being the age of the procedure an important component of the decision. Emerging genetic therapies, including gene therapy and genome editing, may become available in the future, especially considering that robust preclinical work has been already performed in this area. Despite the progress in the treatment of MPS VII, several unmet needs still persist, and supportive therapy continues to play a major role in the management of this challenging disease.

## Abbreviations

4-MU, 4-methylumbelliferyl; BMT, bone marrow transplantation; CNS, central nervous system; CS, chondroitin sulfate; DMMB, dimethylmethylene blue; DS, dermatan sulfate; ERT, enzyme replacement therapy; GAG, glycosaminoglycan; GUS,  $\beta$ -glucuronidase; GVHD, graft-versus-host disease; HLA, human leukocyte antigen; HS, heparan sulfate; HSCT, hematopoietic stem cell transplantation; IV, intravenous; LC-MS/MS, liquid chromatography–tandem mass spectrometry; M6P, mannose-6 phosphate; MDRI, multi-domain responder index; MPS, mucopolysaccharidosis; NIHF, non-immune hydrops fetalis; rhGUS, recombinant human  $\beta$ -glucuronidase; uGAG, urinary glycosaminoglycan.

## Disclosure

The authors report no conflicts of interest related to this work.

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