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Review Article

Several Musculoskeletal Issues in Patients Affected by Mucopolysaccharidoses: Effectiveness of Pharmacological Therapies

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Abstract

Background: Mucopolysaccharidoses (MPSs) induce accumulation of Glycosaminoglycans (GAGs) in different tissues which leads to musculoskeletal manifestations and visceral/neurological involvement.

Objective: This literature review aims to analyze the effectiveness of current and potential treatments for musculoskeletal issues inherent to each type of MPS.

Methods: A Medline search through PubMed was carried out for articles and treatment guidelines on MPSs published in English at least for the past twenty years. The references are reported for each single article, producing both recommendations about the drugs approved for the treatment of MPSs and information's on recent trials of experimental techniques.

Results: Enzyme Replacement Therapy (ERT) and Hematopoietic Stem Cell Transplantation (HSCT) are the longest practiced therapies and, despite having influenced the course of MPSs, the complete healing has never yet been achieved. Potential future strategies, therefore, like Gene Therapy, Substrate Reduction Therapy, Chaperone Therapy and Anti-Inflammatory Therapy, are being tested as different pharmacological approaches to disease.

Conclusions: MPSs are rare disabling disorders and targeted/effective long-term therapeutic strategies are necessary as regards the treatment of limiting musculoskeletal feature. Neonatal screening for MPS should be also considered a future goal, which would allow an early diagnosis, ensuring an immediate start of treatments in order to slow down the natural course of pathology.

Keywords: Mucopolysaccharidoses; Enzyme replacement therapy; Haematopoietic stem cell; Rhodamine B; Infliximab

Introduction

Mucopolysaccharidoses (MPSs) are a rare group of genetic metabolic disorders caused by a deficiency or malfunctioning of enzymes responsible for the correct degradation of Glycosaminoglycans (GAGs) [1]. Enzyme lack produces lysosomal accumulation of GAGs and consequent their excretion in the urine, leading to development of different somatic and neurological features. MPSs are classified from I to IX based on the enzyme wanting and their incidence is about 1 in 20,000-25,000 born [2]. These diseases are fatal in severe forms, but a normal lifespan can be reached for attenuated disorders. In Table 1 main characteristics of each MPS are reported. Different therapeutic strategies have been evaluated for MPSs treatment. Enzyme Replacement Therapy (ERT) and hematopoietic Stem Cell Transplantation (HSCT) have shown significant benefits for many types of MPS. Most important results of these therapies have been demonstrated for visceral organs, but skeletal dysplasia, lesions in corneas, heart valves, cognitive impairment and, above all, blood-brain barrier penetration, are still difficult to treat and resolve. Gene therapy, Substrate Reduction Therapy (SRT) and chaperone therapy are some novel treatment options which could modify the course of some MPS in the future, but many studies are still needed. In this review we summarize different treatments especially for musculoskeletal impairment in MPSs, from the oldest to the most innovative therapy.

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Materials and Methods

This literature review aims to analyze the effectiveness of current and potential treatments for musculoskeletal issues inherent to each type of MPS. Key words used for research have been: mucopolysaccharidoses, enzyme replacement therapy, idursulfase, haematopoietic stem cell, rhodamine, infliximab. A Medline search through PubMed was carried out for articles and treatment guidelines on MPSs. One hundred twenty nine articles have been selected. All the studies written in the English language, published at least for the past twenty years, analyzing only musculoskeletal problems and concerning the pharmacological treatment of MPSs were included. Articles written in other languages, dating back over twenty years, involving visceral issues and including surgical and non-conservative treatments were excluded.

Enzyme Replacement Therapy (ERT)

In ERT, intravenous infusions are carried out to supply insufficient or absent enzyme by exogenous administrations [3]. Food and Drug Administration (FDA) approved laronidase for MPS I in 2003, idursulfase for MPS II in 2006, galsulfase for MPS VI in 2005,

Table 1: Main characteristics of Mucopolysaccharidoses [128].

MPS Type	Incidence	Musculoskeletal features	Other major features
MPSI			
Hurler	1:100000	Disproportional short stature, joint stiffness/ contractures, claw hands, odontoid hypoplasia, thoracolumbar kyphosis, scoliosis, hip dysplasia, genu valgum Carpal tunnel syndrome, trigger fingers Dysostosis multiplex	Psychomotor retardation, coarse facial features, macrocephaly, spinal cord compression, corneal clouding (vision impairment), hearing loss, organomegaly, cardiac (valve, coronary artery) disease, respiratory disease, recurrent ENT infections, umbilical/inguinal hernias, hydrocephalus
Hurler–Scheie		Intermediate between MPSI Hurler and MPSI Scheie	Intermediate between MPS I Hurler and MPS IScheie
Scheie		Mild short stature, joint stiffness/contractures, carpal tunnel syndrome, trigger fingers	Corneal clouding, cardiac (valve) disease, umbilical/inguinal hernias, organomegaly, spinal cord compression, hearing loss
		Dysostosis multiplex	No psychomotor retardation
			Only mild coarsening of facial features
MPSII			
Hunter A severe	1:100000–150 000 (male subjects)	Disproportional short stature, joint stiffness/ contractures Thoracolumbar kyphosis, hip dysplasia	Psychomotor retardation, coarse facial features, macrocephaly, respiratory disease, cardiac disease, retinal degeneration (no corneal clouding), hearing loss, organomegaly
		Carpal tunnel syndrome, trigger fingers Dysostosis multiplex	Gastrointestinal symptoms (diarrhoea), umbilical/inguinal hernia Hydrocephalus, spinal cord compression
			Melanocytosis
HunterBmild		Mild disproportional short stature, joint stiffness/ contractures	Hearing and vision impairment
		Carpal tunnel syndrome Dysostosis multiplex	Gastrointestinal symptoms (diarrhoea), sleepapnoea No psychomotor retardation
MPSIII			
SanfilippoA–D	1:70000	Short stature, mild joint stiffness/contractures	Severe psychomotor deterioration and behaviour problems: progressive dementia, aggression, hyperactivity, sleeping disorders Seizures
		Genu valgum Dysostosis multiplex	Mildsomaticmanifestations:coarsefacialfeatures,hirsutism,organomegaly,hearingloss
MPSIV			
MorquioA–B	1:200 000	Disproportional short stature, hypermobile joints	Hearingloss,cornealclouding,cardiac(valve)disease,organomegaly,cariesteeth,spinalcordcompression
		Odontoid hypoplasia, thoracolumbar kyphosis, scoliosis, pectus carinatum, coxa valga, genu valgum, pes planus Dysostosis multiplex	No psychomotor retardation and no coarse facial features
MPSVI			
Maroteaux–Lamy	1:250000-600000	Disproportional short stature, joint stiffness/ contractures (mainly hips)	Corneal clouding, hearing loss, hernias, organomegaly, cardiomyopathy, cardiac valve disease, respiratory disease Spinal cord compression
		Kyphoscoliosis, hip dysplasia, genu valgum, odontoid hypoplasia, carpal tunnel syndrome, trigger fingers, dysostosis multiplex	Coarse facial features
			No psychomotor retardation
MPSVII			
Sly	1:250000	Disproportional short stature, joint stiffness/ contractures	Wide spectrum of severity: from severe hydrops fetalis to less severe pheno types with (mild) psychomotor retardation, coarse facial features, corneal clouding, hernias, organomegaly, cardiac (valve) disease, spinal cord compression
		Odontoid hypoplasia, thoracolumbar kyphosis, dysostosis multiplex	
MPS IX			
Hyaluronidase deficiency		1 Case reported	Mild facial changes (e.g, flattened nasal bridge) No psychomotor retardation
		Short stature, no joint stiffness	

elosulfase alfa for MPS IVA in 2015 and vestronidase alfa for MPS VII in 2017 [4-6].

MPS I

In 2003, laronidase, a recombinant human alpha L iduronidase (rhIDUA), has been the first ERT approved [7]. In 2004, Wraith et al. [8] in a Phase 3 of a double blind, placebo-controlled study, showed effects of human alfa-L-iduronidase (rhIDUA) so ministration in patients with mean age of 16 years. They received randomly laronidase 0.58 mg/kg or placebo weekly for 26 weeks. At the end of the study, urinary GAGs and hepatomegaly were significantly reduced, should motility and elbow extension were increased, Forced Vital Capacity (FVC) and distance in 6 minutes walking test (6MWT) were improved (5.6% and 38 m respectively). In 2009 Clarke et al. [9] with an open label extension study, rolled the same 45 patients to receive laronidase weekly for 3.5 years. At the end of the therapy, patients manifested benefits in daily life and activities with: GAGs normalized in 15% of patients, reduced hepatomegaly, less apnea/hypopnea, improvement in visual acuity and in 6 MWT, more joint mobility, in particular of shoulder range motion and knee flexion/extension. Kakkis et al. [10] showed first and, unlike all the others authors, amelioration about two upper joints simultaneously: elbow extension and shoulder flexion, with an optimal impact on upper limb movements and, consequently, on self-care during Activities of Daily Life (ADL).Wraith et al. [11] in 2007 carried out a study to evaluate efficacy of ERT in younger patients and they selected 20 subjects with severe subtypes of MPS I aged less than 5 years. All patients received laronidase 0.58 mg/kg weekly for 52

weeks: hepatomegaly, hypopnea and myocardiopathy were improved without benefits about height and weight. Many treated patients (95%) developed anti-laronidase IgG antibodies leading to a lower reduction of urinary GAGs. Actually, the International Consensus Panel [12], about treatment of MPS I, recommended laronidase in patients who have: age >2 years, age <2 years and attenuated phenotype and age <2 years, severe phenotype and Intelligence Quotient (IQ) less than 70. It was clear that as soon as possible the treatment was undertaken, more obvious benefits patients would get. About that, Gabrielli et al. [13] reported data on ERT infused at first stage of disease: they compared effects of laronidase therapy initiated at the age of 5 months in a presymptomatic boy with attenuated form of MPS I, to effects on his older sister who began therapy at 5 years of age, when typical MPS I features were developed. After 5 years of follow up, the boy showed no manifestations as joint disease, coarse facies, and organomegaly, dysostosis multiplex and cardiopulmonary impairment, except for corneal clouding. In contrast, MPS features in older sibling were stabilized or improved, but not deleted.

MPS II

The replacement enzyme approved and used for MPS II is Idursulfase, a recombinant human iduronate-2- sulphatase (rhI2S) [14]. Muenzer et al. [15] in 2006 carried out a phase 2/3 of a double-blind study with 96 patients enrolled who received placebo or idursulfase 0.5 mg/kg weekly or idursulfase 0.5 mg/kg Every Other Week (EOW) for 53 weeks, with final evaluation of a composite outcome (6 MWT and FVC combined). The best results were in the group which received the enzyme weekly, above all with a significant increase in 6 MWT (weekly score: +18.96 ± 6.47; EOW score: 12.86 ± 6.17). Both groups recorded most evident results about hepatosplenomegaly with an average reduction of 23%, urinary GAGs reduced from 44% and 52% and IgG anti-idursulfase antibodies found in 47% of patients. Then, 94 patients were enrolled into an open label, extension trial and after 20 months of treatment with idursulfase once weekly, showed improvement in FVC, shoulder extension/flexion, prepubertal growth velocity and maximum increase in the 6 MWT [16]. Sohn et al. [17] evaluated effects of idursulfase beta, on 31 patients from 6 to 35 years of age, in a Phase I/II clinical trials and showed an important increase in the 6 MWT with improvements in endurance. Moderate effects on joint mobility and respiratory function have been obtained, but no serious adverse effects were reported. Australian guidelines [18], recommended ERT for MPS II only in patients with attenuated phenotypes and when disease was amenable for improvement; Hunter Syndrome European Expert Council, instead, believed all MPS II cases subject able for a 18 month trial of ERT, except for extremely advanced disease from the beginning. Also for MPS II, early initiation of ERT was strongly recommended. Tilki-Szimanska et al. [19] showed that a child treated within 3 months of age developed, as only somatic feature, a mild deformity of one vertebra after 3 years of therapy without other clinical signs. Tajima et al. [20] reported a case of two Japanese siblings with a rare re arrangement between *IDS gene* and *IDS 2 pseudogene*. The older brother began ERT at 3 years of age and the younger at 4 months of age. After 32 months of therapy, the younger patients displayed almost none somatic and musculoskeletal features compared to older, in which persisted. When the younger sibling was 5 years old, only mild dysostosis multiplex with slow progression were developed. In conclusion, newborn and early ERT have proved a better impact on bone growth and musculoskeletal signs.

MPS III

This MPS, Sanfilippo Syndrome, presents different neurological symptoms with neurocognitive and behavioural decline, but somatic features are relatively mild. Four subtypes have been delineated: A-B-C-D. For MPS IIIA and MPS IIIB ERT has been attempted. In MPS III the deficient enzyme is heparan N-sulphatase. The replacement therapy used a recombinant protein N-sulfo glucosamine sulfo hydrolase used with a monoclonal antibody against the human insulin (HIR-MB) [2]. In a Phase I/II study, the administration of recombinant human heparan N sulfatase was intrathecal with moderate adverse effects. Urinary GAGs were reduced and only 50% of patients presented anti rhHNS antibodies, but neurocognitive impairment was not stopped and different patients ended in a semi-vegetative state. No musculoskeletal benefits were obtained [21]. In MPS IIIB the deficiently so some enzymes N-Acetyl-Alpha-Glucosaminidase (NAGLU). Two strategies of intrathecal injection have been attempted: in the first, recombinant NAGLU was fused with IGF II. The fusion protein rh NAGLU-IGF II, after intrathecal administration in mice, showed a 60% reduction in GAGs levels and, above all, a high uptake by neurons [22]. In the second strategy, the fusion protein was HIRMAb-LL-NAGLU (mono clonal antibody against the human insulin receptor combined with rhNAGLU) and was intravenously injected in a Rhesus Monkey showing the most uptake in liver, milder uptake in the heart and lung and minimum uptake in muscle and bones. More over only 1% of fusion protein injected was located in brain. Actually, NAGLU-IGF II and HIRMAb-LL-NAGLU are only potential therapeutic options for MPS IIIB patients [23].

MPS IVA

The replacement enzyme approved in 2014, from FDA and European Medicines Agency (EMA) [24], for MPS IVA (Morquio Syndrome) treatment, is elosulfase alfa (recombinant form of human Galactosamine N-Acetyl-6-Sulfatase, GALNS). In an open label phase I/II trial, 20 patients received weekly infusions and was noted an important improvement in the 6 MWT, above all in patients who travelled a distance <200 m. The Three-Minute Stair Climbing Test (3MSCT) was not improved by ERT but in the Cardiopulmonary Exercise Test (CPET) an increase in exercise capacity after 25 weeks was highlighted. Moreover, substantial decrease of urinary GAGs was achieved. All treated patients showed antibodies after 120 weeks of treatment, without reduced clinical benefits [25,26]. Unfortunately, the early and prolonged ERT administration (within 5 years of age) did not improve musculoskeletal features as hypermobility and hyperlaxity, spinal compression, short stature and altered bone and cartilage development [27,28]. Recently, Sawamaoto et al. [2] reported a moderate impact of ERT on cartilage lesions and bone dysplasia: in fact, after 30 months of ERT, vacuoles were still present in bone affected by pathology. In conclusion, ERT had moderate effect for cardiopulmonary features of MPS IVA, but no benefits for skeletal manifestations. To date, to overcome limited effects of ERT on bone, bone targeting strategy has been developed: GALNS enzyme tagged with amino acid peptide particles, E6 and D6. In model mouse, tagged GALNS remained Longley in circulation, reaching 10-20 times higher activity than native enzyme. Thus, GAG accumulation resulted markedly reduced in articular cartilage and in bone compartment with consequent improvement of critical skeletal dysplasia. Actually, bone targeting ERT could be a potential future strategy for MPS IVA [29-31].

MPS VI

In 2005 galsulfase has been approved by FDA for MPS VI, Maroteaux-Lamy Syndrome [32]. Now is available in USA, Europe and Australia and it is recommended as the first line therapy because is safer than HSCT, historically accepted for MPS VI [33]. In a Phase I/II clinical trial seven patients received Naglazyme (galsulfase) for 48 weeks in two concentrations (0.2 and 1 mg/kg) and were registered: decreased GAGs urinary and, above all, increase of shoulder range of motion and reduced pain and stiffness [34]. In a Phase II open label trial, Harmatz et al. [35] reported a significant increase of distance in 6 MWT and 12 MWT, respectively of 80% and 138%. An important improvement was noted in 3 MSCT. Efficacy and safety of Naglazyme was tested in a Phase 3 randomized, double blind clinical trial with 39 patients rolled for 24 weeks. All patients reported a rapid decrease in their urinary GAGs level. The primary endpoint analyzed was 12 MWT with improvement of 92 m; the secondary endpoint was the 3 MSCT with increase of 5.7 ± 2.9 stairs. These results were better than data observed in the placebo group. Walking endurance and 3 MSCT ability resulted significantly improved. In contrast, no benefits of Naglazyme infusion were reported about musculoskeletal features, somatic symptoms and bone growth. All MPS VI patients developed antibodies after 4 to 8 weeks of treatment and the most common adverse effects registered were pyrexia, dyspnea, nausea and rigors, but all these events have been controlled by antihistamines, corticosteroids, anti inflammatory agents or by steroid pretreatment [36]. Early infusion of ERT in the first moment of life (between 6 weeks and a year old) slowed the progressive evolution of some skeletal anomalies: growth and facial dysmorphism, low stair-climbing ability and poor walking endurance. However, a total reversal of musculoskelatal pathology and consequent manifestations have not been reported to date [33].

MPS VII

In 2017 vestronidase alfa has been approved for MPS VII, also known as Sly Syndrome [6]. It is caused by deficiency of beta glucuronidase that leads to tissue accumulation of chondroitin sulphate. This syndrome is characterized by neurocognitive impairment, behavioral problems and musculoskeletal deformities as dysostosis multiplex, reduced growth and coarse facies. The replacement enzyme was infused in a 12 year old boy, every 2 weeks for 24 weeks. After this time, the cardiopulmonary function was the most improved one: supplemental oxygen reduced to 28%, 80 min twice per day tolerated without ventilator and without carbon dioxide increased, electrocardiogram abnormalities decreased after 14 weeks of therapy. Hepatosplenomegaly was normalized, endurance improved and behavioral disturbance reduced. Moreover, less fatigue and a reduced wheelchair use were noted. No musculoskeletal benefits have been registered and somatic symptoms were not improved [37]. Qi et al. [6] evaluated pharmacokinetic and pharmacodynamic of vestronidase in 23 patients and reported a complete drug absorption in tissues through injection of 4 mg/kg EOW with subsequent GAGs urinary reduction and increase efficacy of treatment. In a MPS VII mouse model, "long circulating ERT" has been tested, namely, a chemically recasted b Glucuronidase (GUS), to make latter more resistant to clearance by mannose and M6P receptors (PerT-GUS), evidencing prolonged half life (over 18h), compared with normal enzyme (half life less than 30 min) [38]. PerT-GUS showed remarkable amelioration in bone lesions of ribs, spine and tibia and an improvement in GAGs accumulation in articular chondrocytes [39]. These data showed that PerT-GUS therapy from birth, could significantly attenuate skeletal dysplasia in MPS because, hypotetically, PerT-GUS was able to reduce GAGs storage in macrophages that provide inflammatory factor as TNF -alpha, directly connected to bone disease in MPS disorders [40].

Focus on ERT and Spine Disease in MPSs

Evidence suggests that ERT intravenous injection is able to prevent the progression spinal abnormalities as vertebral dysplasia, disc degeneration and dural thickening. Low findings have been reported to correction of preexisting disease by ERT [41] and animal model results are promising for human comparison. Chiaro et al. [42] referred: attenuation of cervical spine features, increased vertebral bone density, implemented vertebral ossification and normal odontoid process morphology in MPS I dogs treated with ERT within the first year of life. A study on MPS VI cats demonstrated a dose dependent response to ERT with a normalizated length of lumbar vertebrae and trabecular bone density after 6 months of treatment [43]. In conclusion, earlier infusion classically provided better spine findings, despite the difficult diffusion of enzyme with high molecular weight into the disc and the cartilage of the vertebrae that were avascularized [44].

Hematopoietic Stem Cell Transplantation (HSCT)

Hematopoietic Stem Cell Transplantation (HSCT) is a current non-pharmacological option of treatment for MPS. Till now, it has been tested for patients with MPS I, II, IVA and VII, getting a good compliance and therapeutic results. Blood stem cells are withdrawn from bone marrow peripheal blood and umbilical cord blood. It is fundamental to have a donor compatible and, moreover, subject the receiver patient to an immunosuppressive therapy for reducing immune response and the development of patient's rejection of the donor cells [2]. The advantages of HSCT are: treatment "one shot" because, after transplantation, the defected enzyme is secreted permanently without continuous administration, moreover, donor cells are able to penetrate blood-brain barrier compared to ERT. Finally, this therapy could eliminate pre-exisisting immune response against enzyme infused by ERT. Disease features as reduced joint mobility, growth, hepatosplenomegaly, decreased vision, cardiopulmonary and hearing ability are improved by the engrafted cells, but in the cornea, heart valves, avascular cartilage and the bone less results are achieved. This is caused by the inefficient enzyme penetration in the musculoskeletal tissues. Better outcomes have been noted in attenuated than severe forms of MPS [45,46]. Early diagnosis is really important because as soon as possible the treatment is undertaken, all the more optimal benefits could be obtained, above all about skeletal deformities and impaired growth development. In this regard, some trials showed effects of HSCT at birth on skeletal issues. Increased mobility, reduced craniofacial dysmorphism, more rapid and efficient GAGs clearance by storage in joints/bones and clinical amelioration was reported on newborn MPS mice treated [47]. At Tokai University [48,49], moreover, cord blood transplantation from unrelated donors has been experienced, providing a full donor/recipient chimerism and normalized enzyme levels in all treated MPS patients, with a high safety profile and instant availability.

HSCT for MPS I

MPS I is characterized by neuro cognitive impairment, cardiopulmonary disease and skeletal dysplasia. It is the MPS with the greater number of patients subjected to HSCT (600+) and is classically divided in three subtypes: Hurler syndrome, the most severe; Hurler-Scheie syndrome, the intermediate and Scheie

syndrome, the attenuated, also known as MPS V. Hurler syndrome, the most frequent subtype, is characterized by an early progressive neurological decline [50]. In the USA, HSCT is administered as hallmark therapy in patient before 3 years of age and with severe development impairment >70, because it is the only treatment able to reduce intellectual decline [51,52]. In 2004, Staba et al. [48] showed that from unrelated donors cord blood cells could be transplanted into subjects of maximum 2 years of age affected by Hurler syndrome, gettings lowdown of neurological decline and improved growth velocity with bone anomalies stabilized. Hite et al. [53] in 2000 indicated a favorable response to HSCT of odontoid dysplasia in MPS I patients; Spina et al. [54] in 2018 confirmed this result and also a substantial reduction of claw hands and general musculoskeletal dysplasia. Langereis et al. [55] as results of an international consensus procedure, indicate that genu valgum, gibbus deformity, hip dysplasia and other skeletal anomalies were less responsive to HSCT than CNS. Benefits was minimum and consequently, pain and limited ambulation were not ameliorated and ADL continued to be difficult [56]. Similar data were collected by Schmidt et al. [57] that referred on 19 Hurler syndrome patients, 6.8 years after HSCT, stabilized craniocervical stenosis, odontoid dysplasia and joint mobility. Nevertheless, complications like carpal tunnel syndrome, genu valga and gibbus deformity continued to decline although worsening was slowed in some conditions, as thoracolumbar kyphosis. Actually, in several world countries, newborn screening for Hurler syndrome is routinary practices, thus the diagnosis and the treatment are early carried out. The first month after birth is the best time frame to effective prevention of bone anomalies in patients with severe MPS I form [58]. ERT is considered the standard therapy for patients with mild spectrum of disease because patients with attenuated form do not have symptoms before 3 and within 12 years of age. It has been supposed that ERT and HSCT combination could improve clinical features. HSCT was found to reduce formation of antibodies developed after ERT. The co administration has been tolarated without graft failure or complications [59]. Australian guidelines [60] recommended ERT in patients with MPS I for 12 weeks before stem cell transplant and 15 to 17 weeks post-transplant. In conclusion, for MPS I, HSCT had a successful impact on neurocognitive, cardiopulmonary impairment and on hepatosplenomegaly but a limited impact was registered on corneal degeneration and, above all, on musculoskelatal symptoms.

HSCT for MPS II

MPS II, Hunter Syndrome, is the second MPS with highest number of patients underwent HSCT (150+). It is characterized by visceral organs impairments, skeletal dysplasia and neurocognitive decline presents in the childhood and that continues to worsen over the years, stopping in the adolescence [2]. In Japan, HSCT has been the target therapy for MPS before approval of ERT, like a combination treatment. Tanaka et al. [61] demonstrated improvement in ADL, urinary GAGs reduced and decreased brain atrophy on Magnetic Resonance Imaging (MRI). In 2017, Barth et al. [62] reported a case of MPS II patient with severe form of disease subjected to HSCT from umbilical cord at 70 days of age. A follow up of 7 years underlined attenuation of neurocognitve decline and normal growth charts at 7 years of age. No musculoskelal benefits were rised. Impact of ERT and HSCT on urinary GAGs was compared in retrospective study of MPS II patients. DS and diHS-0S (Dermatan Sulfate and derivatives) levels were significantly reduced in patients underwent a combination of ERT/HSCT. HSCT improved brain lesions and long-term MRI findings compared to no effects by ERT [63]. Patel et al. [64] compared effect of HSCT and ERT on growth and they concluded that a limited impact on weight and height were obtained with both techniques. However, HSCT provided a higher ADL scores between late ERT and early HSCT had a successful impact on ADL than late HSCT. In conclusion, HSCT preserved some intellectual function and slightly improved ADL, especially when patients were treated at early stage of MPS, but a little impact was reported on musculoskeletal dysplasia and motor impairment.

HSCT for MPS III

MPS III, also known as Sanfilippo Syndrome, with 4 subtypes (A-B-C-D), is characterized by accumulation of heparan sulphate over all in the brain leading to severe neurocognitive impaiment, intellectual decline and behavioural disturbance. In contrast, somatic symptoms are secondary and attenuated compared to other MPS [65]. Actually, there is not standard therapy for MPS III. HSCT had no significant impact on this disease though it crosses BBB and, despite transplantation has been conducted within 2 years of age, no benefits on neurological decline have been showed [66,67].

HSCT for MPS IV

MPS IVA, Morquio syndrome, is caused by a deficiency of N-acetylgalactosamine 6-sulfatase (GALNS) causing accumulation of keratan sulphate present primarily in bone and cartilage. It is characterized by joint laxity, hypermobility, dwarfism and skeletal dysplasia. Respiratory problems are common in this MPS but, compared to other subtypes, neurocognitive function do not worsen throughout lifespan [68,69]. Different studies demonstrated amelioration with treatment by HSCT. Chinen et al. [70] showed in a 15 years old boy improvement on sleep apnea, ADL, lumbar bone mineral density (increased by 50%) and GALNS activity normalized at 9 years post transplant. Ambulation and movement were increased and, consequently, quality of life and mood level enhanced. Hypothetically, bone growth could be raised and stabilized if patients undergo HSCT in the first years of life. In 2016 Yabe et al. [71], reported allogeneic HSCT in 4 patients with MPS IVA. In all 4 patients Graft versus Host Disease (GVHD) were not developed and GALNS enzyme activity were normalized in all cases. HSCT improved the clinical ADL in MPS IVA patients and scores reached in ADL were elevated thereafter. The patient of this group who underwent HSCT when 4-year-old had the best ADL score, thus early treatment could have a more successful influence on bone growth. In 3 cases, surgical intervention post-HSCT seemed to be no fundamental and only one patient underwent a bilateral osteotomy after transplantation. Although HSCT had a considerable impact in walking, stair climbing, physical endurance and hand movement, a limited improvement on bone growth of MPS IVA were registered because HSCT were infused only at the end of bone growth. Wang et al. [72] reported improvement in hyperlaxity, hypermobility, thoracic anomalies, height, attenuated spinal cord compression and sleep apnea during one year after HSCT. No rejection and GVHD have been registered. A significant amelioration of joint hypermobility were also noted at the Shangai Clinical medical center, where 9 children's with MPS IVA, underwent HSCT and only for two of them surgery for spinal compression and genu valgum were necessary. In conclusion, HSCT could be an effective therapeutic strategy for Morquio syndrome, reducing surgical intervention and ameliorating motor pattern, ADL and respiratory function [2,68].

HSCT in MPS VI

MPS VI, Maroteaux-Lamy Syndrome, is caused by arysulphatase

deficiency leading to dermatan sulphate and chondroitin sulphate accumulation. Symptoms include: dysostosis multiplex, short stature, cranio facial anomalies, cardiopulmonary impairments but noneurocognitive decline in most patients [73]. In the past, HSCT had been the only specific treatment for MPS VI, but it is not universally available because there are few donors and high risk of morbidity and mortality. In the USA, HSCT is recommended only after ERT failure. The European Group for Bone Marrow Transplantation showed, after HSCT, risk of mortality from 10% to 25% [74]. Some studies (Herskhovitz et al. [75] and Summers et al. [76] reported attenuated craniofacial dysmorfism, improvement in cardiac symptoms, uncertain results about cornea and visual acuity in 4 patients treated by HSCT. Skeletal manifestations worsened but posture and ambulation improved. In contrast, other fundings showed no amelioration in dysostosis multiplex and cardiopulmonary function because HSCT did not provide to enzyme penetration into distal tissues. Data are conflicting because patients underwent HSCT have already showed progressive decline throughout lifespan thus it is recommended to use HSCT at childhood before somatic manifestations [2,77]. In conclusion, HSCT for MPS IV have showed limited impact on skeletal defects and somatic features that tended to progression [78].

HSCT for MPS VII

MPS VII, Sly syndrome, is a rare disorder caused by beta Glucuronidase Deficiency (GUSB), resulting in accumulation of chondroitin sulphate primarily. Clinical features are in common with MPS I, but without neurological disfunction in most patients. Life expectancy is reduced because patients often present hydrops fetalis at birth [79,80]. HSCT for MPS VII demonstrated a limited impact on linear growth and neurological failure. In contrast, symptoms successfully attenuated are: activity enzyme considerably increased almost normal range and, above all, amelioration in motor function was noted [81]. Currently, only 8 patients have been treated in the world since 1996. Sisinni et al. [82] in 2018 reported a case of 2 years old patients treated twice with HSCT. Data were: enzyme levels normalized, neurocognitive decline attenuated and, moreover, skeletal anomalies improved.

Gene Therapy

Gene therapy is an experimental approach for MPS treatment because it could promote the correction of defected enzyme and the permanent secretion in the brain and musculoskeletal tissues. Gene therapy presents three potential advantages: first, the cross correction system of lysosomal enzyme leads to their reuptake into several tissues and organs after genetic modification; second, a low level of normal enzyme is sufficient to have improvement in clinical features and, finally, since only one gene caused each MPS, the defected enzyme is well known. There are two different approaches in gene therapy: ex vivo and in vivo gene therapy [2]. In ex vivo gene therapy, autologous hematopoietic stem cells are genetically manipulated *ex vivo* and, then, they are transplanted into the patients. With this technique, rejection and GVHD are dramatically reduced [83]. *In vivo* gene therapy, the copy of defective gene is inserted into a recombinant vector which is injected systematically or infused in depot organs, getting a target function of corrected enzyme in specific sites. Regarding brain pathology, the administration of vector-mediated gene into Central Nervous System (CNS), caused a reduction of lysosomal storage in mice brain with improvement of neurocognitive decline, but low diffusion and duration of vectors are still largely problematic [84-87]. Data about dogs and mice indicate that this experimental, systemic therapy, can achieve clinical improvements, attenuation of bone lesions, normalization of morphometric parameters and bone content [88]. In Table II were ported and compared benefits and negative aspects of ERT, HSCT and Gene Therapy respectively.

MPS I

Plasmids and sleeping beauty transpose on system (non viral vectors) increased IDUA activity, reduced hepatosplenomegaly, GAGs accumulation, corrected growth plate anomalies in femur and tibia and caused thinning of the bone in the zygomatic arch, without remarkable outcomes on diameters reduction of diaphyseal bone areas because of short term exposition of these vectors in bone lesions [89,90]. Gamma Retroviral Vectors (RV), in mice, provided a supraphysiological enzyme activity level in serum and several tissues, reaching in newborn mice treated an increase up to 28 fold greater than wild type, maintained for 1.8 years. Thereby, this enzyme bioavaibility improved facial and chest anomalies, joint laxity, and deformation of normal angles of the elbows, carpi and phalanges. Above all, average life increased [91,92]. In spite of this supraphysiological IDUA activity levels, after 24 months of follow up, no amelioration in lengths of vertebrae and no significative reduction of toracolumbar kyphosis were achieved. Promising findings have been reported by combined therapy with HSCT-Lentivectors. This combination provided a supraphysiological enzyme activity level and a normalization of bone length and volume in the humerus and femur, more clinically evident than infusion of wild type HSC [93].

MPS IVA

Gamma-retroviral and Adeno-Associated Virus (AAV) have been tested as gene therapy in Morquio syndrome [94]. Despite in mice increase in GALNS activity and decrease of GAGs accumulation in several tissues were noted, no amelioration has been evidenced in bone tissue. Almeciga-Diaz therefore have experimented a "bone-targeting system" with AAV-GALNS (adeno-associated virus plus GALNS) combined to AAV-SUMF1 (adeno-associated virus plus Sulfatase Modifying Factor 1), reaching a remarkable enhance in GALNS activity mostly in bone cells, with an increased activity by 33%. However, biodistribution of vectors in bone remained ineffective and poor. Thus, an attempt was made modifying vector capsid with insertion of a short acidic amino acid peptide providing a greater vector delivery into hydroxyapatite, a fundamental component of the bone matrix. This strategy allowed to reach an enzyme activity of about 42% of wild type enzyme levels [95,96].

MPS VI

A MPS VI feline underwent AAV2/8 mediated liver gene transfer between 5 and 50 days after birth, reporting reduction of GAGs levels in cortical bone osteocytes, improvement in joint mobility, long bone size and cervical spine abnormalities [98]. In 2012 Ponder et al. [99], attempted gene therapy on newborn MPS VI cats infusing a gamma retroviral vector that delivered *ARSB gene*. After 8 years of treatment they reported a supraphysiological enzyme activity level persistent in different tissues. In spite of this degeneration of cervical spine were not attenuated and joint mobility, articular cartilage erosion and long bone size were not ameliorated. In conclusion, a supraphysiological enzyme activity levels did not provide an optimal resolution of musculoskeletal impairment of MPS VI.

MPS VII

Xing et al. [100] tested in newborn dogs with Sly Syndrome, retroviral GUSB gene therapy from birth and followed for up to 11

Table 2: Comparison of current therapeutic options for Mucoplysaccharidoses [2].

	ADVANTAGES	DISADVANTAGES
ERT	Lowrisk	Expensive
	No limitation of age and/or compromise of health	Requirescontinuousadministration (typicallyweekly or bi-weekly)
	Ease of administration	Short enzymehalf-life
		Does not cross the bloodbrainbarrier
		Lesseffect in bone, heartvalve, cornea
HSCT	Permanenttreatment	Rejection
	Continuoussecretion of the enzyme	GVHD
	Able to penetrate blood–brain barrier and some skeletalsymptoms	Availability of matcheddonoroftendifficult
	Eliminate pre-existing immune responseagainstinfusedenzyme by ERT	Risk of mortality
		Need a special facility
GENE THERAPY	Permanent treatment	Off-target gene effect
	Continuoussecretion of the enzyme	Potential immune responseagainst a vector and gene product
	Potentially low cost	Unknown long-termeffect
	Potentiallyable to cross blood–brain barrier	Can not eliminate pre-existing immune responseagainstinfusedenzyme by ERT
	No matcheddonorrequired	

years. Dogs responded with rise of circulating enzyme, increased mobility, quality of articular bone, correction of most bone anomalies (acetabulum dysplasia, coxofemoral and patella luxation, synovial hyperplasia) and increased lifespan. Nevertheless, vertebral bone lesions and intervertebral disc degeneration were not attenuated because of the inability of GUSB to diffuse in spine. Macsai et al. [88] treating MPS VII mice through lentiviral gene therapy, showed outcomes in partial normalization of vertebrae bone mass and morphometric parameters. However, no significant results about femur bone length and chondrocytes architecture were underlined.

Experimental Strategies

Substrate reduction therapy

Substrate Reduction Therapy (SRT) is an experimental approach that aims to slow GAGs synthesis rather than removing the defective enzyme and downgrades GAGs. This therapy is oral but, compared to ERT attenuating clinical features, molecules used in SRT are able to cross BBB because of their low mass and weight, there by neurological decline and symptoms are considerably decreased [101].

Rhodamine B, a fluorescent molecule, is an indirect-non specific GAGs synthesis inhibitor and showed *in vitro* to reduce GAGs synthesis in MPS IIIA and VI and to improve some neurocognitive features in MPS IIIA mice [102,103]. Actually, toxicity of Rhodamine B is not well known and other clinical trials have to carry on in the future [105]. Gene Expression-Targeted IsofLavone Therapy (GET IT) is another potential strategy for MPSs treatment whose peculiarity is slowing production of substrates that cannot be totally removed. It is based on genistein, an extract purified from plant isoflavone that reduces GAGs synthesis and accumulation, inhibiting phoshorylation of Epidermal Growth Factor Receptor (EGFR) [105]. Piotrowska et al. [106] in 2008 showed efficacy of GET IT to attenuate neurological symptoms in MPS III patients, but no outcomes in motor response have been reported. In an open label study of 2011 Marucha et al. [107] underwent seven patients with MPS II treated with geniste in at the dose to 5 mg/kg daily showing, after 6 months of oral administration, improvement in active and passive shoulder flexion and abduction in all patients (from 10° to 30°). Less increase in ROM of other joints as wrist and elbow has been reported, but not in all cases treated. Four patients reached improvement also in motor of lower limbs, though restrictions in this district were lower than upper limbs because walking acts as an inbred rehabilitation that increased movement and impaired GAG storage in the joints. Compared to effects of ERT on motor response, GET IT showed greater outcomes. In fact, intravenous administration of 0.5 mg/kg idursulfase weekly for 12months in 10 MPS II patients (ages between 21 and 53 years) have shown a little improvement of joints ROM by 8°-19° [108]. Alcade-Martìn et al. [109] reported minimum decrease of joint stiffness after 12 months of ERT in children with Hunter Syndrome. In conclusion, benefits of GET IT about motor response were better than ERT in patients with MPS II, thus this therapy could be a good option of treatment also combined with ERT. Dziedzic et al. [110] and Kaidonis et al. [111] suggested SRT as a potential and effective future strategy for MPS because presented various advantages, including no adverse reactions reported and high compliance for patients because it was an oral therapy, with a good impact on the quality of life. Actually, SRT is not approved for MPS, instead, has been approvated for other lisosomal storage disorders, as gaucher disease type I and Niemann-Pick type C disease. The therapy approved is Miglustat, a glucosylceramide synthase inhibitor, a precursor of GM2 ganglioside [112,113]. In MPSs, it could attenuate neurocognitive impairment but, Guffon et al. [114] reported no benefits about neurological symptoms in Sanfilippo Syndrome and, to date, no clinical trials have been conducted about effects on mobility in MPS disorders.

Pharmacological chaperone therapy

Pharmacological chaperone therapy is a future proposal of therapy for MPS. It is based on the use of small molecules, pharmacological chaperones that interact with deficient substrates in the Golgi and endoplasmic reticulum, leading to the correct protein folding in the ER [115].

These molecules present several advantages and disadvantages. Advantages are: no immunogenicity, oral administration, ability to cross BBB, success on phenotype, low enhance of enzyme activity [116]. Disadvantages are: ultra rare adverse reactions, limited outcomes reported to date and only some mutations responsive [116,117]. Studies are carrying on the combination with ERT to enhance efficacy of the treatment [118]. Pharmacological chaperone therapy has been tested for MPS II (sulfate disaccharide from heparin) and MPS IIIC (glucosamine), reaching correct enzyme activity amelioration. To date, no results have been reported about benefits on bone, cartilage and joint mobility [119,120].

Anti inflammatory therapy

Inflammation is a hallmark in the skeletal anomalies of MPS because GAGs accumulation in bone, extracellular matrix and cartilage stimulates the release of pro-inflammatory factors as TNF alpha, MIP, IL 1-2-5 with consequent cartilage degradation, osteoarthritis and skeletal dysplasia [121]. Anti-inflammatory and immuno suppressive drugs are able to reduce metabolic inflammation processes that worsen MPS features. These agents can be administrated alone or combined with other systemic treatment. Anti inflammatory drugs have different mechanisms of action [42]. Chiaro et al. [42] tested ERT combined with simvastatin, cholesterol - lower product with anti inflammatory features, on MPS I dogs from seven days after birth, for preventing cervical disc pathology but they showed a limited impact of this treatment. PPS (Pentosanpoly Sulfate Sodium) is a drug with important anti-inflammatory properties, approved by FDA, for interstitial cystitis, used for phlebitis and thrombosis prophylaxis and able to reduce significantly pain on patients with knee osteoarthritis [123]. Scuchman et al. [124] showed that this oral and subcutaneous medication, administered in MPS VI rats from birth, had a successful impact to reduce skeletal and cartilage inflammation and increased vertebral bone density and joints mobility. Subcutaneous PPS could be more effective because of higher bioavaibility. PPS stimulates proliferation and chondrogenic differentiation of mesenchymal precursor cells derived from adult human bone marrow. In several MPS disorders PPS could attenuate clinical impairment reducing GAGs accumulation, musculoskeletal inflammation and stimulating chondrogenesis in tissues. Finally pain due to osteoarthritis decreased, quality of life and social function resulted improved [124]. An immunosuppressive agent tested for MPS is Infliximab, a TNF A inhibitor. TNF A is a cytokine that primarily promotes inflammation in MPS with increase of RANKL (Receptor activator of nuclear factor kappa-B ligand) and other pro-inflammatory mediators in synovial fibroblasts and chondrocytes of MPS VI rats. Infliximab reduced chondrocytes apoptosis, but no results on bone and mobility have been registered till GAGs accumulation was present. Eliyahu et al. [126] evaluated benefits of ERT combined with Infliximab reporting restoration of IL-1, reduction of apoptotic markers in articular chondrocytes, down regulation of TNF A, attenuation of synovial hyperplasia and, moreover, a successful impact on cartilage development. In the future it will be fundamental to develop "target therapies" able to influence bone growth properly and directed to specific musculoskeletal tissues and cells, modulating osteogenic growth factors such as BMPs, TGF b, IHH and WNTs and their signaling pathways. Targeting specific medication to cartilage is possible through nano particles and future studies could test new techniques specifically for intervertebral disc, bone and epiphyseal cartilage that are strongly compromised in MPSs [127,128].

Conclusions

MPSs are genetic disorders with various phenotypic characteristics, different severity, different course and different therapeutic response. To date, ERT has been approved for MPS I, II, IVA, VI and VII and HSCT has been administered worldwide in thousands of MPS patients with a broad spectrum of disease presentation. ERT could be a better choice at least in the short term; HSCT in patients healthier and affected by mild forms of MPS, due to the higher mortality rate for subjects in severe conditions. Despite the benefits of both therapeutic options, manifold disadvantages have been reported and the resolution of musculoskeletal problems remains an unmet challenge to date. Gene therapy, experimental approaches, like bone targeting therapy and combination strategies, may be optimal novel treatments, but multiple researches will have to be developed with consequent application of the best therapeutic results in the clinical practice. It will be essential to focus attention on the implementation of newborn screening for MPS all over the world in order to cure the pathology at an early stage, not just slowing its progression, especially about somatic features and musculoskeletal anomalies, the most disabling for the patient's autonomy. The current therapeutic options are able to minimize damage for most patients from consequences of the disorder and to better the QOL. It seems that treatment results are more effective the earlier therapy is started, which may encourage the implementation of newborn screening for these diseases. The involvement of musculoskeletal system in MPS remains an unsolved, serious problem and powerful, innovative strategies such as bone target therapy may prove to be directives for MPSs in the next future.

Authors Contribution

The authors confirm contribution to the paper as follows: Study conception and design: Rossana Gnasso, Irene Iommazzo; Data collection: Rossana Gnasso, Giulio Magliulo, Carlo Ruosi; Analysis and interpretation of results: Rossana Gnasso, Bruno Corrado; Draft manuscript preparation: Rossana Gnasso. All authors reviewed the results and approved the final version of the manuscript.

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