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Review

Update of treatment for mucopolysaccharidosis type III (sanfilippo syndrome)

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ABSTRACT

Mucopolysaccharidosis III (Sanfilippo syndrome, MPS III) is caused by lysosomal enzyme deficiency, which is a rare autosomal recessive hereditary disease. For now, there is no approved treatment for MPS III despite lots of efforts providing new vision of its molecular basis, as well as governments providing regulatory and economic incentives to stimulate the development of specific therapies. Those efforts and incentives attract academic institutions and industry to provide potential therapies for MPS III, **including enzyme replacement therapies, substrate reduction therapies, gene and cell therapies, and so on**, which were discussed in this paper.

1. Introduction

Mucopolysaccharidosis III (MPS III, Sanfilippo syndrome), an autosomal recessive lysosomal storage disorder, was characterized by progressive mental retardation and behavioral problems (Kong et al., 2020; Valstar et al., 2008). Deficient enzymes involved in the lysosomal degradation of the heparan sulfate (HS), member of glycosaminoglycan, caused series of clinical symptoms, especially in central nervous system (CNS). Based on deficiency of enzymes, MPS III comprised four described subtypes, which were recognized as MPS III type A (OMIM #252900), type B (OMIM #252920), type C (OMIM #252930), and type D (OMIM #252940) (Heon-Roberts et al., 2020).

The incidence of MPS III was estimated to range from 1 to 9 per 1,000,000 live births, which was less than the incidence of MPS II and MPS I (Khan et al., 2017; Zelei et al., 2018). Although treatments for MPS I and II have been developed and approved to date, there was no treatment for MPS III that has been approved by any government in the world (Tambuyzer et al., 2020). To speed up the development of innovative therapies for MPS III, several regulatory initiatives have been approved by governments of world, such as conditional marketing authorization in the European Union, accelerated approval and priority review in United States, and so on (Tambuyzer et al., 2020).

There were lots of reviews of treatment for MPS III. Valstar et al. (2008) discussed five directions of therapies for MPS III: enzyme replacement therapy (ERT), substrate reduction therapy (SRT) , gene therapy (GT), hematopoietic stem cell transplantation (HSCT) and enzyme enhancement therapy (EET) (Valstar et al., 2008). SRT could contain the contents of EET, which was rarely mentioned. In subsequent years, more and more drugs that have been tired to treat patients with MPS III were discussed, such as genistein, recombinant human heparan N-sulfatase (rhHNS), and so on (Andrade et al., 2015; Fedele, 2015; Gaffke et al., 2018; Jakobkiewicz-Banecka et al., 2016). In recently, Pearse et al. (2020) described clinical results of therapies for MPS III, such as genistein, BMN 250 and other therapies (Pearse and Iacovino, 2020). In this review, we not only updated most recent results from clinical trials of therapies for MPS III, but also reviewed some new therapies which reported recently, such as trehalose, combined therapies and so on.

2. Enzyme replacement therapy (ERT)

MPS III was caused by deficiency of enzymes, so ERT, compensation for abnormal enzymes, is a reliable way to treat MPS III (Jones et al., 2020).

An open-label phase I/II dose-escalation safety trial (NCT01155778) showed rhHNS through intrathecal administration was well tolerated in

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12 patients with MPS IIIA (Jones et al., 2016). A phase IIb randomized trial (NCT02060526) was carried out to assess the potential clinical efficacy of rhHNS. Final results of this clinical trial were reported recently: although rhHNS reduced HS level in all treated patients through intrathecal administration, primary neurocognitive endpoint was not met (at least three responders in a dosing group) (Wijburg et al., 2019). One of reasons that caused such unsatisfactory results was that concentration of rhHNS could not keep sustainably (Wijburg et al., 2019). Find a way to prolong the half-life period of rhHNS in the serum may get a positive result.

Other group tried to keep ERT drug sustainably to improve the efficacy. Avoiding mannose 6-phosphate receptor interaction, SOBI003, chemical modified recombinant human N-sulfoglucosamine sulfohydrolase (CM-rhSGSH), could reduce uptake of the enzyme into peripheral tissues and facilitate distribution of CM-rhSGSH in CNS (Fig. 1A) (Gustavsson et al., 2019; Janson et al., 2020). Main therapeutic target organ for MPS III is CNS, lack of peripheral efficacy would still correct disease significantly. After repeated intravenous (IV) administration, CM-rhSGSH had sustained and higher concentration in serum, cerebrospinal fluid (CSF) and brain interstitial fluid, which was in accordance with reduction of HS, improvements of neuroinflammation (Gustavsson et al., 2019; Janson et al., 2020; Makower et al., 2019). Positive results gave manufacture confidence to set up clinical trials for testing SOBI003 as a potential treatment for MPS IIIA patients (NCT03423186 & NCT03811028).

Chinese hamster ovary cells or a human cell line could not generate recombinant human alpha-N-acetylglucosaminidase (rhNAGLU) with mannose 6-phosphate during post-translational processing, so rhNAGLU for MPS IIIB patients is limited by inadequate cellular delivery (Weber et al., 2001; Zhao and Neufeld, 2000). BMN 250 is a fusion protein, consisting of human NAGLU fused with insulin-like growth factor 2 (IGF2), which was expressed in Chinese hamster ovary cells (Fig. 1B) (Aoyagi-Scharber et al., 2017). Because IGF2 could transit BMN 250 directly to the lysosome, intracerebroventricular (ICV) delivery of BMN 250 throughout the CNS replaced the malfunction NAGLU to reduce HS (Aoyagi-Scharber et al., 2017). Based on compelling preclinical findings of BMN 250 in mouse and canine models (Aoyagi-Scharber et al., 2017; Ellinwood et al., 2017; Matthew et al., 2018), several clinical trials were carried out to evaluate the safety, tolerability, and therapeutic potential of BMN 250 as a potential therapy for MPS IIIB (https://www.clinicaltrials.gov: NCT02754076 and NCT03784287). Because animal model of MPS III B showed blood-brain barrier impairment, IV and ICV delivery of BMN 250 were compared to confirm value of ICV (Grover et al., 2020).

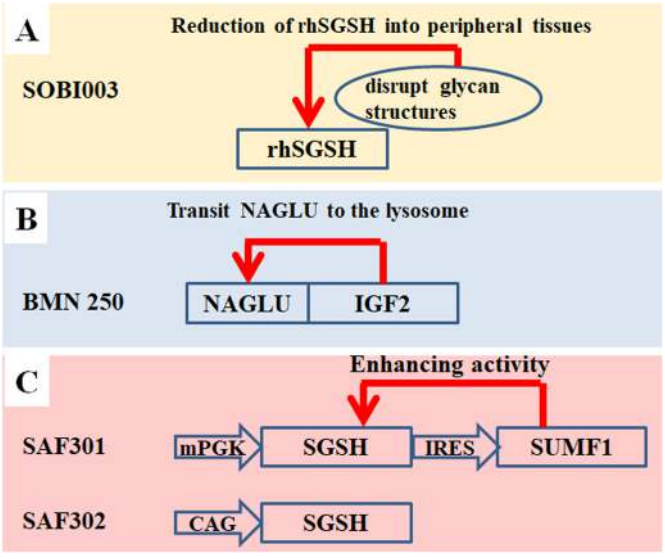

Fig. 1. Therapeutic mechanism of some treatments for MPS III. A: chemical modification helped SOBI003 to keep sustained and high concentration. B: insulin-like growth factor 2 (IGF2) allowed BMN 250 was transited directly to lysosome. C: sulfatase modifying factor 1 (SUMF1) could enhance activity of SGSH (SAF301); cytomegalovirus early enhancer/chicken β actin (CAG) promoter let *SGSH* gene produce more product of transcription (SAF302). mPGK: mouse phosphoglycerate kinase. IRES: internal ribosome entry site.

In cellular models, BMN 250 also showed interesting results: under conditions of limited exposure duration, BMN 250 was taken up more rapidly than NAGLU without IGF2 and showed a dose-dependent reduction of total HS. With sustained exposure, NAGLU without IGF2 could clear lysosomal HS as well, which gives a hint that drug delivery systems may be an option for MPS IIIB (Prill et al., 2019; Shirley, 2020; Yogalingam et al., 2019).

Although final results of the phase 1/2, open-label clinical study of IV rhNAGLU (SBC-103) did not show expected efficacy, data of BMN 250 in cell and animal models gave the confidence to continue trying ERT for MPS IIIB treatment (Whitley et al., 2019). A phase 1/2, open-label study demonstrated that ICV-administered BMN 250 was well tolerated without treatment-emergent serious adverse events and showed good clinical effect (keeping total HS of CSF and liver volume in normal range; improvement in developmental quotient) (Muschol et al., 2018).

3. Substrate reduction Therapy (SRT)

Small molecules were attractive as therapeutic agents for MPS III, because they had following advantages: generally low-cost, stability, able to cross the blood-brain barrier, non-immunogenicity, controlled dosing and multiple routes of administration. At first, small molecules were used to reduce synthesis of HS, i.e. genistein (Piotrowska et al., 2006). Both ERT and SRT were used to establish a new balance in metabolism of glycosaminoglycan. Then small molecules were found to have more ways to relieve MPS III patient's symptoms, such as anti-inflammatory, autophagy activation and so on (Guo et al., 2019; Lotfi et al., 2018).

Genistein, a type of isoflavonoid, has diverse biological activities, such as anthelmintic and antioxidant effects, as well as inhibition of several cancers (Kim, 2019; Li et al., 2020). Piotrowska et al. (2006) reported genistein could inhibit tyrosine-specific protein kinase activity of epidermal growth factor receptor, which regulated expression of genes coding for enzymes involved in glycosaminoglycan production through initiating a specific kinase cascade (Piotrowska et al., 2006). Results from other groups confirmed this observation and supported to initiate clinical trials to test genistein as a potential therapy (Arfi et al., 2010; Malinowska et al., 2009). Those studies, which used low dose genistein (5–15 mg/kg/day) to treat MPS III patients, showed no serious adverse effects and variable neurocognitive outcomes (de Ruijter et al., 2012; Delgadillo et al., 2011; Marucha et al., 2011; Piotrowska et al., 2008). High dose treatment of genistein in mice showed good efficiency and safety, then clinical trial with high dose genistein was started (Malinowska et al., 2010). Kim et al. (2013) initiated an open label study to assess the safety of high dose genistein treatment, which showed no serious adverse events (Kim et al., 2013). All these clinical trials were open label uncontrolled, which was not gold standard for assessing the efficiency of treatments (Sedgwick, 2014).

A double blinded, randomized, and placebo-controlled phase 3 trial was initiated to explore the safety and effectiveness of high-dose genistein in children with MPS IIIA, B and C since 2014 (GENiSIS 2013). Twenty-one patients were enrolled and given 160 mg/kg/day genistein or placebo for one year, followed by a year of open-label treatment period with 160 mg/kg/day genistein. Although no significant adverse side effect was observed, results from this trial do not support that off-label high-dose genistein could be a potential treatment for children with MPS III, because there was no measurable clinical benefit and no significant reduction in CSFHS (https://www.clinicaltrialsregister.eu/ctr-search/trial/2013-001479-18/results). Such negative results

reminded researchers to find new ways or new drugs.

Anakinra, an interleukin-1 receptor antagonist, was used to treat autoinflammatory disorders, including rheumatoid arthritis and neonatal-onset multisystem inflammatory disease (Cavalli et al., 2020). Chronic neurodegeneration, clinical phenotype of MPS III, is typically accompanied by inflammation, which could lead to disease progression through production of inflammatory mediators. Preventing the development of the neurocognitive phenotype in MPS IIIA mice by blockade of interleukin-1 showed anakinra as a potential therapy for MPS III, which gave sponsors confidence to start a random clinical trial (NCT04018755) (Parker et al., 2020). Another anti-inflammatory drug, pentosan polysulfate, was tried in mouse model with MPS IIIA and showed positive results: attenuation of neurobehavioral deficits and reduction of biomarkers for neuroinflammation and neurodegeneration in brain (Guo et al., 2019).

Miglustat (N-butyldeoxynojirimycin), an inhibitor of ceramide glucosyltransferase, showed good safety and tolerability data with a stabilization of neurological manifestations in most Niemann-Pick disease Type C patients, which gives a hint that miglustat may improve/stabilize the clinical manifestations of MPS III (Patterson et al., 2010, 2020). A randomized, double-blind, placebo-controlled, mono center, institutional, phase IIb to III study showed miglustat treatment had an acceptable safety profile without any improvement/stabilization of behavior problems in patients with MPS III (Guffon et al., 2011). Varying baseline characteristics may cause poor treatment outcomes in the first clinical trial of miglustat in MPS III, so animal models were used to provide a homogeneous baseline for improving efficacy test (Kaidonis et al., 2016). In MPS IIIA murine, learning ability and innate fear response were improved by miglustat treatment, which gives confidence to test efficacy of miglustat treatment by clinical trials (Kaidonis et al., 2016).

Autophagic impairment has been linked to neurodegenerative diseases mainly based on two mechanisms: 1. Loss of autophagy in neurons causes reduced recycling of altered cellular components; 2. increased aggregation of amyloid-β, tau, and α-synuclein, which are closely associated with a variety of neurodegenerative diseases (Heon-Roberts et al., 2020). Autophagy activation drug may be an option for MPS III treatment. Despite genistein could correct Huntington's Disease Phenotype in cell model by inducing autophagy, no measurable clinical benefit of clinical trials did not support that genistein was a potential drug for MPS III (Pierzynowska et al., 2018). Trehalose, a disaccharide with protein-stabilizing and autophagy-enhancing properties, may be another therapy option for MPS III. Trehalose has been tried to treat patients with neurodegenerative disease (i.e. Machado-Joseph disease) and showed positive results (Noorasyikin et al., 2020; Zaltzman et al., 2020). There was no clinical trials of trehalose for MPS III patients, but mouse model of MPS IIIB, treated with trehalose, showed longer life, less hyperactivity and anxiety, vision maintenance and inflammation reduction (Lotfi et al., 2018). Animal and cell experiments showed that trehalose effects relied on transcription factor EB and an active autophagy pathway (Lotfi et al., 2018).

In addition to above drugs, other small molecules were also considered to treat MPS III, such as rhodamine B, coenzyme Q10 and dimethyl sulfoxide (Matalonga et al., 2014; Moskot et al., 2019; Roberts et al., 2007).

Traditional SRT inhibited accumulation of HS at protein level, RNA suppression approaches (i.e., antisense oligonucleotides, ribozymes, and RNA interference), based on high specification and low toxicity, showed a new way to reduce accumulation of HS.

As we know, small interfering RNA (siRNA) has been tested in cell model of MPS III and showed positive results (Beneto et al., 2020a; Canals et al., 2015; Dziedzic et al., 2010). siRNA could be a highly promising therapeutic agent for MPS III, but siRNA based therapy was seriously hampered by a number of challenges, including poor stability, short blood circulation, low blood-brain barrier penetration, and so on (Rosenblum et al., 2018). Enclosed by nanocapsules may be a reliable way to keep stability and bypass blood-brain barrier (Van de Vyver et al., 2020; Zou et al., 2020).

Screening of small molecule drugs, based on cell models, is powerful tool to find new SRT for MPS III. CRISPR/Cas9, an efficient tool for precise genome editing, was used to edit healthy human induced pluripotent stem cell line to generate cell line of MPS III, which could provide more cell models to screen suitable drugs (Beneto et al., 2020a; Beneto et al., 2019; Beneto et al., 2020b).

4. Gene therapy (GT)

GT, introducing genetic material into cells to compensate for abnormal genes, was a potential method to correct disease (Lundstrom, 2019; Verma and Somia, 1997). In vivo GT for MPS III, based on Adeno-associated virus (AAV), has been reviewed recently (Marco et al., 2019). Lentiviral-mediated correction of clinical phenotypes has also been developed for MPS IIIA and MPS IIIB (Ellison et al., 2019; Holley et al., 2018). The main steps of in vivo GT and ex vivo GT were showed in Fig. 2.

Recovery of enzyme activity is the main purpose of GT: Over 8.5% of normal enzyme activity will be sufficient to improve neuropathology and behavior of MPS IIIA mice model that was treated with GT (Sergijenko et al., 2013). There were at least two ways to pass this threshold (8.5%): higher enzyme activity (SAF301) and more product of transcription (SAF302) (Fig. -1C) (Gray et al., 2019). SAF301 and SAF302 were all in process of clinical trial (NCT01474343, NCT02053064 and NCT03612869). Results of a phase I/II trial of SAF301 (NCT01474343) showed good safety with moderate improvements in behavior, attention and sleep disturbances (Tardieu et al., 2014). Long term follow up of these MPS IIIA patients (NCT02053064) were ongoing and would offer more data of safety and efficacy in the future. Although clinical trial data of SAF302 (NCT03612869) was not published, mouse model showed that SAF302 offered a greater benefit in vivo than SAF301 (Gray et al., 2019). Animal model data of SAF302 increased motivation to find better promoter for vector design.

Another potential GT for MPS IIIA was ABO-102, a self-complementary AAV9-based vector with human SGSH gene that was promoted by ubiquitous U1a promoter, which has been used in two clinical trials (NCT02716246 and NCT03300453). Interim results of NCT02716246 showed long-term safety and tolerability profile, as well as clinical neurological benefit in the youngest patient who was treated before neurodegeneration was advanced (Flanigan et al., 2020). The same manufacturer of ABO-102 also operated other clinical trials for MPS IIIB with ABO-101 (www.abeonatherapeutics.com).

Among all tested serotypes, AAV9 and AAVrh10 showed the highest neurotropism following intra-CSF delivery, meanwhile both of them could cross the blood-brain barrier efficiently (Belur et al., 2020; Bey et al., 2020). These characteristics allowed AAV9 and AAVrh10, as benchmark vectors, to be used frequently in vector design for MPS IIIA, such as SAF301 (AAVrh10), ABO-102 (AAV9) and so on (Marco et al., 2019). AAV-TT, new AAV capsid based on AAV2, demonstrated more effective distribution within the brain than AAV9 and AAVrh10 (Tordo et al., 2018). MPS IIIC mice treated by AAV-TT vector with HGSNAT (acetyl-CoA:alpha-glucosaminide N-acetyltransferase) showed better results than the one treated by AAV9 vector with HGSNAT, such as correction of pathological behavior, anti-neuroinflammation and so on (Tordo et al., 2018). These results will let more researchers design GT vectors with AAV-TT.

The first mouse model of MPS IIID was reported in 2017 and treated by AAV9 vector carrying GNS (N-acetylglucosamine-6-sulfate sulfatase) which was controlled by ubiquitous cytomegalovirus early enhancer/chicken β actin promoter. Corrected pathological storage of HS, resolved neuroinflammation and other solid evidence supported that GNS-encoding AAV9 vector was a therapeutic option for MPS III (Roca et al., 2017).

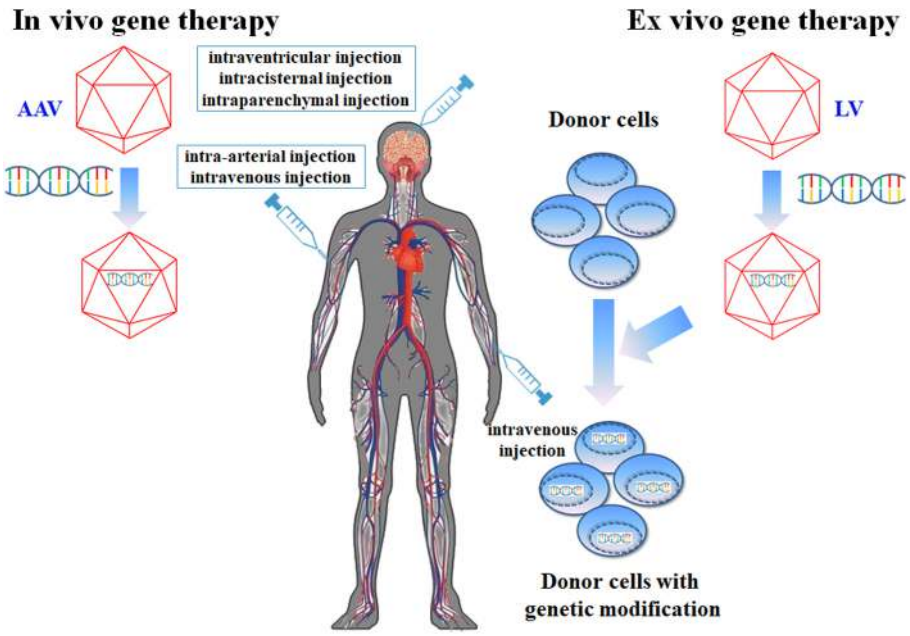

Fig. 2. In vivo and ex vivo gene therapy. AAV: Adeno-associated virus vector. LV: lentiviral vector.

5. Hematopoietic stem cell transplantation (HSCT)

HSCT has been used to treat patients with various lysosomal diseases and showed gratifying results (Leal et al., 2020; Stok et al., 2020), however, HSCT for MPS III patients yielded conflicting results. In 1990s, few clinical trials for MPS III showed poor cognitive outcome, even deterioration of cognitive function despite successful HSCT (Klein et al., 1995; Shapiro et al., 1995; Sivakumur and Wraith, 1999). Other reports showed that HSCT could stabilize or even improve clinical manifestations which were better than untreated siblings (Kurtzberg et al., 2005; Prasad et al., 2008; Vellodi et al., 1992). In 2020, one case with MPS IIIA, followed up for 8 years after HSCT treatment, was reported to have better cognitive skills and motor function than other 6 untreated patients (Kohn et al., 2020). The authors also admitted that they could not draw any universally applicable recommendations from this case, because of limited number of case and other genetic factors that could not be excluded (Kohn et al., 2020).

Genetic modification gives a chance to improve efficacy of HSCT, which could be classified as ex vivo GT (Fig. 2). Like in vivo GT, most of ex vivo gene therapies introduced enzyme with normal function through lentiviral vector (LV) to treat MPS III. Langford-Smith et al. (2012) used wild-type (WT) donor cells, WT donor cells with LV-expressing SGSH (LV-WT-HSCT) and MPS IIIA cells with LV-expressing SGSH to treat MPS IIIA mice model. LV-WT-HSCT could bring more benefits to mice model (Langford-Smith et al., 2012). Other reports confirmed the safety and efficacy of ex vivo GT in animal model with MPS III (Bigger BW et al., 2018; Ellison et al., 2019; Holley et al., 2018; Parker et al., 2020; Sergijenko et al., 2013). Based on the safety and efficacy data, the first clinical trial to explore the safety, tolerability and clinical efficacy of ex vivo GT in MPS IIIA patients was registered as NCT04201405 (www.clinicaltrials.gov).

6. Discussion

Although there was no treatment that had been approved by any government in the world till now, more and more drugs and therapies showed the potential that could arrive at the end of victory. All privately and publicly funded clinical trials, registered on www.clinicaltrials.gov, of ERT, SRT and GT were listed in Table 1. The main contents of this review were summarized in Fig. 3.

Table 1
Clinical trials of ERT, SRT and GT (www.clinicaltrials.gov). ERT: Enzyme Replacement Therapy. SRT: Substrate reduction therapy. GT: gene therapy. rhHNS: recombinant human heparan N-sulfatase; rhNAGLU: recombinant human alpha-N-acetylglucosaminidase. IGF2: insulin-like growth factor 2. CMV: cytomegalovirus. SGSH: N-sulfoglucosamine sulfohydrolase. AAV: adeno-associated virus. NCT: national clinical trial.

NCT Number	Status	Conditions	Interventions
ERT			
NCT02350816	Terminated	IIIA	HGT-1410 (rhHNS)
NCT01155778	Completed	IIIA	rhHNS
NCT02060526	Completed	III	rhHNS
NCT01299727	Terminated	III	rhHNS-10 mg rhHNS-45 mg rhHNS-90 mg
NCT03784287	Enrolling by invitation	IIIB	AX 250/BMN 250 (rhNAGLU-IGF2)
NCT02754076	Active, not recruiting	IIIB	AX 250/BMN 250 (rhNAGLU-IGF2)
NCT02324049	Completed	IIIB	SBC-103 (rhNAGLU)
NCT02618512	Terminated	IIIB	SBC-103 (rhNAGLU)
NCT03811028	Active, not recruiting	IIIA	SOBI003
NCT03423186	Completed	IIIA	SOBI003
SRT			
NCT04018755	Active, not recruiting	III	anakinra
GT			
NCT03315182	Recruiting	IIIB	rAAV9.CMV.hNAGLU
NCT01474343	Completed	IIIA	Genetic: SAF-301
NCT02053064	Completed	IIIA	Genetic: SAF-301
NCT03612869	Recruiting	IIIA	LYS-SAF302
NCT04088734	Recruiting	IIIA	ABO-102
NCT02716246	Recruiting	IIIA	ABO-102
NCT03300453	Completed	IIIB	rAAV2/5- hNAGLU
NCT04201405	Recruiting	IIIA	Autologous $CD34^+$ cells transduced with a lentiviral vector containing the human SGSH gene

According to our review, main purpose of therapies for MPS III was to get rid of unnecessary HS. However, besides reducing accumulation of HS, anti-inflammatory and autophagy activation should be other purposes of therapies for MPS III (Parker and Bigger, 2019). Neuroinflammation is a clinical phenotype of MPS III, which has been reported

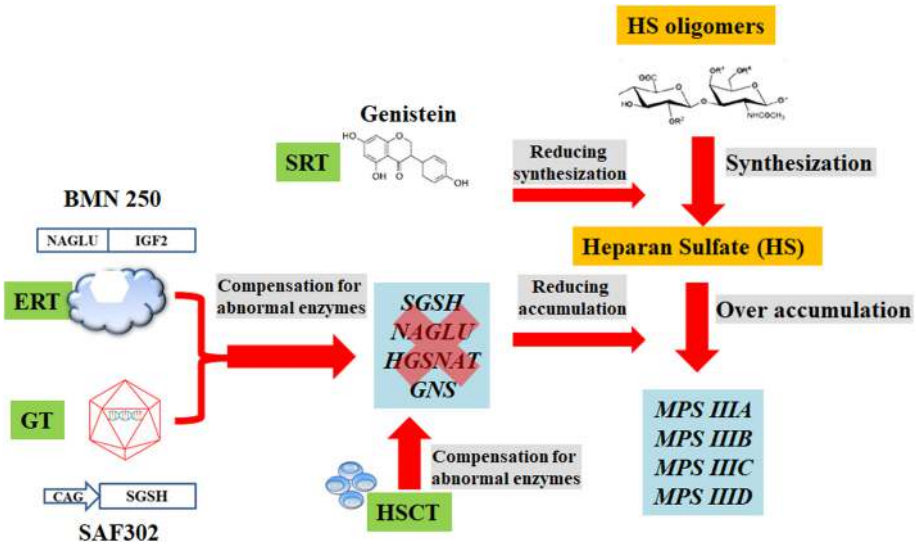

Fig. 3. Therapies for MPS III. ERT: enzyme replacement therapy; SRT: substrate reduction therapy; GT: gene therapy; HSCT: hematopoietic stem cell transplantation.

by many groups (Arfi et al., 2011; Ausseil et al., 2008). Although exact form of HS which was required to activate an immune response was unclear, soluble HS fragments in extracellular matrix may assume a Toll-like receptor 4 agonist role and promote an immune response to caused neuroinflammation (Goodall et al., 2014). Anti-inflammatory drugs and autophagy activation drugs could not cure patients with MPS III; however, these drugs were combined with other therapies, which may improve quality of life and slow disease progression.

Because SRT could not compensate for abnormal enzymes, it was impossible for SRT to cure MPS III, but SRT may relive the life of MPS III. HSCT yielded contradictory results, which was worth more exploration. ERT and GT have been considered the most promising routes for therapeutic intervention in MPS III, which was caused by enzyme deficiency; however, there was no treatment which had reliable clinical results to be approved by governments. Combination therapies may be the future for MPS III treatment. Some reports reported combination therapies, which showed better results than mono-drug, such as ex-vivo GT combined with prednisolone for MPS IIIB, triple combination therapy (miglustat with curcumin and ibuprofen) for Niemann-Pick type C1, and so on (Holley et al., 2018; Williams et al., 2014). In addition to anti-inflammatory drugs, other forms of combination therapies would be tried to offer a better curative effect for MPS III patients, such as SRT with ERT, ERT with GT and so on.

Lots of efforts provided new visions of therapies for MPS III, as well as governments provided regulatory and economic incentives to stimulate the development of specific therapies. Those efforts and incentives attracted academic institutions and industries to provide more and more potential therapies for MPS III. We will see the approved treatment in the near future.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

Data from patients can be made available from the corresponding author after discussion with the Institutional Review Board.

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Authors' contributions

KWJ and YYQ collected and analyzed related articles, then wrote the manuscript. ZJ and LC collected related articles. DYX supervised data and manuscript. MY supervised analysis of related articles and revised writing of the article. All authors read and approved the final manuscript.

Declaration of competing interest

The authors declare that they have no competing interests.

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