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Innovative Therapeutic Approaches for Mucopolysaccharidosis III

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Mucopolysaccharidosis III (MPS III, Sanfilippo syndrome) is a rare autosomal recessive disease caused by a deficiency of one of four enzymes involved in the degradation of glycosaminoglycan (GAG). The resultant cellular accumulation of GAG causes various clinical manifestations. MPS III is divided into four subtypes depending on the deficient enzyme. All the subtypes show similar clinical features and are characterized by progressive degeneration of the central nervous system. A number of genetic and biochemical diagnostic methods have been developed. However, there is no effective therapy available for any form of MPS III, with treatment currently limited to clinical management of neurological symptoms. Main purpose of the treatment for MPS III is to prevent neurologic deterioration. Because conventional intravenous enzyme replacement therapy (ERT) has a limitation due to inability to cross the blood-brain barrier, several innovative therapeutic approaches for MPS III are being developed. This review covers the currently developing new therapeutic options for MPS III including high dose ERT, substrate reduction therapy, intrathecal or intraventricular ERT, fusion protein delivery using bioengineering technology, and gene therapy.

Keywords: Mucopolysaccharidosis III, Sanfilippo syndrome, Treatment

Introduction

Mucopolysaccharidosis III (MPS III, Sanfilippo syndrome) is a rare autosomal recessive disease caused by a deficiency of one of four enzymes involved in the degradation of heparan sulfate. Lysosomal accumulation of heparan sulfate results in celluar dysfunction. MPS III is classified into four subtypes depending on the deficient enzyme: MPS IIIA (N-sulfoglucosamine sulfohydrolase, also known as sulfamidase or heparan sulfate sulfatase); MPS IIIB (N-alpha-acetylglucosaminidase); MPS IIIC (heparan acetyl-CoA:alpha-glucosaminide N-acetyltransferase); MPS IIID (N-acetylglucosamine-6-sulfatase)[1-3]. The clinical manifestations are similar in all subtypes and characterized by progressive degeneration of the central nervous system (CNS). Typical somatic features of MPSs may be present, although milder than in other types of MPSs. Patients with MPS III usually present between the age of 1 and 6 years with developmental delay and/or behavioral problems including hyperactivity and aggression[4,5]. Neurologic deterioration progresses to a vegetative state and death can occur anywhere between the early teens and the sixth decade[5,6]. Although intravenous enzyme replacement therapy (ERT) enabled to improve somatic symptoms in several types of MPS (MPS I, II, IVA, VI, and VII), ERT is not effective therapeutic approach for patients with MPS III. Because of blood brain barrier (BBB), the infused enzyme cannot delivered into CNS and cannot prevent neurodegeneration. Therefore new therapeutic approaches for MPS III is needed. Recently, several clinical and preclinical trials for MPS III are in progress. This review covers the development of innovative therapies for MPS III.

High dose ERT

Intravenous injection of high dose enzyme (as much as 20 times of conventional intravenous ERT) has been tried because the drug dose for conventional intravenous ERT cannot cross the BBB. A report demonstrated that high dose intravenous ERT has

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been reduced the lysosomal storage in CNS and improved neuropathology in murine model of MPS I[7]. Although high dose intravenous ERT has tried in murine model of MPS IIIA, this strategy showed no effect[8]. Indeed, the mechanism how the enzyme protein given intravenously can cross the BBB and be delivered to brain parenchyme is not known at this moment.

Substrate Reduction Therapy

Substrate reduction therapy (SRT) can prevent accumulation of lysosomal storages by reducing the production of the substrate (glycosaminoglycans, GAG) using small molecular chemicals inhibiting former step of substrate production. The chemicals used in SRT are usually small molecules which can be given orally and have potential for crossing BBB. Contrast to the large molecular weight enzyme protein. Rhodamine B, genistein and miglustat have been studied as a candidate molecule for SRT in MPS III.

Rhodamine B nonspecifically inhibits elongation of GAG chain. Rhodamine B could reduce the production of GAG and improved spatial cognition and memory function in MPS IIIA mice[9,10]. However, the mechanism of rhodamine B action should be studied further and the toxicity should be carefully evaluated[11].

Genistein is natural born isoflavone purified from soy. It inhibits the epidermal growth factor-mediated signal pathway, which is needed for expression of genes involving GAG production. Genistein had effects on reduction of accumulated GAGs in various organs including brain, amelioration of neuronal inflammation, and correction of behavioral problems in MPS IIIB mice[12,13]. In addition, a study of 10 patients with MPS III showed decreased accumulation of GAG and improved cognitive function 1 year after treatment[14,15]. However, despite the continued treatment, the effect decreased after two years of treatment. Therefore, the long-term efficacy of genistein is still unclear. Nonetheless, this study suggests that genistein may be a candidate agent for SRT[12-15].

Miglustat (Zavesca®) is a drug approved for the treatment of Gaucher disease type 1 and Niemann-Pick C disease by inhibiting the glucoceramide synthase enzyme to reduce the synthesis of glucocerebromide. Miglustat was expected to inhibit the synthesis of glucosylceramide, a precursor of GM2 ganglioside, to alleviate the symptoms of neurological degeneration in MPS. However, miglustat in clinical trials of patients with MPS III did not reduce ganglioside, and did not improve cognitive functioning or behavioral disorders[16].

Intrathecal or Intraventricular ERT

Enzyme proteins with high molecular weights cannot pass through the BBB, so they can be administered directly to the CNS by intraventricular or intrathecal injection. Injection of recombinant human N-sulfoglucosamine sulfohydrolase (rhSGSH) directly into the brain or into cerebrospinal fluid (CSF) of MPS IIIA mice has been effective in reducing brain pathology[17,18]. In addition, a study of MPS IIIA canine model also showed a reduction in GAG accumulation in brain tissue[19]. Based on these promising results of preclinical studies, The toxicity test was performed on the most similar primate of human, cynomolgus monkey, and the results were reported by Pfeifer et al.[20]. There were no specific clinical side effects associated with the injection of the intrathecal enzyme in this study[20]. No pathologic changes were observed in the spinal cord and meninges, suggesting applicability in the treatment of patients with MPS IIIA. A clinical trial of CSF infusion of rhSGSH is being undertaken. Recently low dose, continuous delivery of rhSGSH using subcutaneously placed osmotic pumps connected to a unilateral intraventricular cannula in the mouse model of MPS III is reported that heparan sulfate in both hemispheres of the MPS IIIA brain and cervical spinal cord is nearly normalized[21].

However, this method may require periodic intraventricular of intrathecal puncture life-long time. And catheter related complications may occur even if an indwelling catheter is inserted. Further studies for development of therapeutic devices will be needed.

Fusion Protein Using Bioengineering Technology

Most of the lysosomal enzymes enter into the cell by binding of Mannose-6-phosphate (M6P) to M6P receptor on the membrane. However, the N-acetylglucosaminidase enzyme produced from the Chinese hamster ovary (CHO) cell line is hardly expresses M6P, making it difficult to enter brain cells through M6P receptors. Therefore, in order to overcome this, insulin-like growth factor II (IGFII) receptor which is widely distributed in neuronal cells is used to deliver the deficient enzyme[22]. Fusion protein is a fusion of α-N-acetylglucosaminidase (EC 3.2.1.50, NAGLU) and a part of the IGFII protein. The fusion protein can be delivered into the CNS by IGFII receptor mediated transport. Because the IGFII receptors are widely distributed in neurons, The NAGLU-IGFII fusion protein binds to the receptor and the enzyme protein is transferred into the brain cells.

Kan et al.[22] reported that NAGLU-IGFII fusion protein was

administered to the brains of MPS IIIB mice, and this fusion protein was endocytosed into the neurons and was effective in reducing accumulation of heparan sulfate in brain tissue.

Gene Therapy

Gene therapy, which replaces the mutant gene by injecting a normal gene into a cell, is attracting as a treatment for MPS III. Because gene therapy is a relatively stable way to transfer enzymes to the brain and skeletal system. Gene therapy using a viral vector as a mediator for transferring a normal gene, or cell-based transfer including stem cell and genetically manipulated-autologous cells had been studied[23].

1. Gene therapy using viral vector

A number of preclinical trials have been performed gene therapy for the treatment of MPS III (mainly IIIA and IIIB) for the past 15 years[24-27]. Because the primary concern of treatment for MPS III is to improve brain pathology, delivering genes directly into the CNS by intraventricular or intrathecal injection using viral vectors, has been studied.

In MPS IIIA and IIIB mouse models, gene therapy was performed by injecting a viral vector containing a normal enzyme gene into the brain and expressing the normal enzyme protein. Through these studies, the GAG accumulation of the brain tissue of the animal model was reduced and neurological function were improved. These gene therapies were particularly effective when performed in the neonatal period[28]. Fraldi et al.[25] reported that adeno-associated virus (AAV) vectors with SGSH and sulfatase modifying factor 1 (SUMF1) injected into the brain improved the brain pathology in MPS IIIA mice. In addition, Cressant et al.[24] reported that gene therapy using AAV vector effectively improved the pathology of the nervous system in MPS IIIB mice.

However, such intracerebral vector injection has a disadvantage in that the volume that can be directly administered to the brain is limited (volume restriction), the vector does not distribute well from the injection site, and the vector remains only around the injection site. In addition, even if the concentration of the enzyme is high at first, the immune response to the normal enzyme protein-producing cell occurs over time, so that the cell expressing the enzyme is destroyed or the inserted gene is inactivated. It is difficult to maintain consistency with therapeutic concentrations. Therefore, there is a disadvantage that an immunosuppressant should be additionally used to the patient to suppress such immune response.

In order to overcome the limitation of direct vector injection in the CNS, a vector such as adenovirus type 9 (AAV9) which can pass through the BBB was injected into the vein to improve both somatic and neurological symptoms[26,28]. Ruzo et al.[26] reported that administration of the AAV9 viral vector intravenously to a MPS IIIA mice improved both CNS pathology and somatic symptoms. For toxicity and safety studies before the clinical trial, Murrey et al.[29] reported that the rAAV9-hNAGLU vector was intravenously administered to the monkey for 6 months had no adverse events, which opened the possibility of proceeding to clinical trials.

Based on the success of preclinical trials, Tardieu et al.[30] conducted a phase I/II clinical trial of gene therapy for adenovirus-associated virus 10 (AAV10) in four patients with MPS IIIA (Clinicaltrials.gov NCT01474343). In this clinical trial, viral vector with normal SGSH and SUMF1 gene were injected into brain via stereotactic neurosurgery and followed up for 1 year. There were no side effects associated with surgery or any immunosuppressive drug use. Brain magnetic resonance imaging revealed no change in brain atrophy in two patients but the brain pathology was progressed in two patients. Neuropsychological evaluation showed that behavioral disorder, attention deficit and sleep disorder were somewhat improved. Notably, it was the most effective in the youngest 2.8 year old patient at the start of the clinical trial, and less effective in patients older than 5 years. Therefore, gene therapy for younger patients before the onset of brain atrophy can be expected to give better results when considering gene therapy.

2. Gene therapy using stem cells

Gene therapy using stem cells is a method of differentiating autologous stem cells into specific cells that are genetically engineered to efficiently produce enzymes[31]. Because autologous stem cells are transplanted, there is no risk of graft-versus-host reaction or difficulties in finding HLA-matched donors. However, it is still an experimental step. Cell-based gene therapy using bone marrow mesenchymal stem cells or neural stem cells has been studied in an animal model of MPSs and reported to reduce lysosomal accumulation in the CNS[32]. It has been reported that gene therapy could be one of the treatment options for MPS III by the results of preclinical and clinical studies. However the important task to be addressed in gene therapy is to develop a safe gene delivery system that can effectively reach the therapeutic level by effectively expressing the normal gene. In addition, prior to clinical trials, studies for selection of appropriate vectors, use of immunosuppressive agents, vector infusion routes, persistence of

effects, and ethical issues should be preceded.

Conclusion

Although MPS III is a rare disorder, it is characterized by progressive neurodegeneration and sufficiently debilitating to patients and parents. Early death in teens occurs in severe phenotype. Innovative therapeutic approaches to overcome BBB are needed due to a limitation of intravenous ERT in patients with MPS III. Successful clinical research is expected to produce positive results in the future as it may lead to the resolution and improvement of major issues, such as poor quality of life due to the regression in neurological functions, shorter life expectancies.

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