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# Current therapies for Morquio A syndrome and their clinical outcomes

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## Abstract

**Introduction—**Morquio A syndrome is characterized by a unique skeletal dysplasia, leading to short neck and trunk, pectus carinatum, laxity of joints, kyphoscoliosis, and tracheal obstruction. Cervical spinal cord compression/inability, a restrictive and obstructive airway, and/or bone deformity and imbalance of growth, are life-threatening to Morquio A patients, leading to a high morbidity and mortality. It is critical to review the current therapeutic approaches with respect to their efficacy and limitations.

**Areas covered—**Patients with progressive skeletal dysplasia often need to undergo orthopedic surgical interventions in the first two decades of life. Recently, we have treated four patients with a new surgery to correct progressive tracheal obstruction. Enzyme replacement therapy (ERT) has been approved clinically. Cell-based therapies such as hematopoietic stem cell therapy (HSCT) and gene therapy are typically one-time, permanent treatments for enzyme deficiencies. We report here on four Morquio A patients treated with HSCT approved in Japan and followed for at least ten years after treatment. Gene therapy is under investigation on mouse models but not yet available as a therapeutic option.

**Expert opinion—**ERT and HSCT in combination with surgical intervention(s) are a therapeutic option for Morquio A; however, the approach for bone and cartilage lesion remains an unmet challenge.

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**Declaration of interest**

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**Keywords**

Morquio A; ERT; HSCT; gene therapy; orthopedic surgery; tracheal obstruction

## 1. Introduction

Morquio A syndrome (Mucopolysaccharidosis IVA, MPS IVA) is a rare lysosomal storage disease. This autosomal recessive disorder is caused by deficiency of the lysosomal enzyme N-acetyel-galactosamine-6-sulfate sulfatase (GALNS). Its deficiency progressively induces accumulation of the glycosaminoglycans (GAGs), keratan sulfate (KS), and chondroitine-6-sulfate (C6S), in multiple tissues, especially, bone, cartilage, heart valves, and cornea [1–4]. The incidence of Morquio A syndrome was reported as 1 per 76,000 births in Northern Ireland and 1 per 640,000 births in Western Australia [5,6].

Morquio A syndrome is characterized by a unique skeletal dysplasia caused by excessive accumulation of KS and C6S. Although most patients with Morquio A generally appear normal at birth, patients often show skeletal abnormality within a few years of age. Skeletal dysplasia with incomplete ossification and successive imbalance of growth results in a short neck and trunk, cervical spinal cord compression, tracheal obstruction, pectus carinatum, laxity of joints, kyphoscoliosis, coxa valga, and genu valgum [7–10]. Radiographic findings show dysostosis multiplex with universal platyspondyly, anterior beaking of the lumbar spine, flaring of the rib cage, tilted ulna, coxa valga, flattering femoral head, and epiphyseal dysplasia of joints. Morquio A is classified as three phenotypes: mild, intermediate, and severe, with systemic bone dysplasia increasing with disease severity [8].

In Morquio A patients, normal cartilage formation is disrupted, presumably as a result of abnormal chondrogenesis and endochondral ossification, leading to poor bone mineralization and abnormal growth. Morquio A patients often become severely handicapped and wheel-chair bound as teenagers [7–9]. Patients with a severe form die of respiratory obstruction, cervical spinal cord complications, or heart valve disease in their 20s or 30s if untreated. Most patients with MPS IVA need multiple surgical procedures including spinal decompression/fusion, leg osteotomies, and hip reconstruction/replacement. Corrective tracheal surgery is often required and anesthesia is high risk throughout their lives.

Early diagnosis of Morquio A is now possible using imaging techniques, molecular analysis, and assay of enzyme activity [11,12]. However, no cure is available and recently described disease modifying treatments need to be perfected. Thus, patients with Morquio A need symptomatic and supportive therapy, either singly or in combination, to slow progression of this disorder. Conventional enzyme replacement therapy (ERT) and hematopoietic stem cell therapy (HSCT) are currently available for patients with Morquio A. In 2014, ERT was approved for patients with Morquio A in the United States and some European countries [13–15]. However, ERT has not yet been shown to improve bone pathology [16,17]. Four HSCT cases of Morquio A patients have been reported to date and all four transplants were successful. Activity of daily living (ADL) for these HSCT patients improved when compared to similar-aged untreated patients [16,18,19]. Gene therapy for Morquio A

syndrome is currently being investigated in a preclinical trial. Gene therapy has the potential to improve bone and cartilage lesions [9,12,20].

Tracheal obstruction is a life-threatening condition and respiratory complications are the main cause of mortality and morbidity in patients with Morquio A [10,21]. Their narrow airway, short neck, and tortuous and redundant trachea make intubation and extubation difficult, and consequently, tracheostomy is often used during surgical procedures. Recently, we have developed a new surgical intervention to reimplant the brachiocephalic artery and remove redundant trachea in patients with Morquio A [22].

In this review, we summarize current therapies available for Morquio A syndrome and its clinical outcomes. We describe the current situation of ERT, HSCT, gene therapy, and orthopedic surgery and provide an update on a new surgical intervention for tracheal obstruction.

## 2. ERT

### 2.1. Conventional ERT for MPS

ERT is one of the most important therapeutic options for patients with MPS, and such therapy has been used over the past three decades for several lysosomal storage disorders. Conventional ERT is either in clinical practice or under clinical trials in patients with MPS I [23], MPS II [24,25], MPS VI [26–29], and MPS VII [30]. ERT has many advantages such as low mortality risk, no age limitation, and no limitation by health condition to start this therapy [16]. However, there are several limitations of conventional ERT for MPS patients: (1) effect of ERT on skeletal dysplasia and central nervous system (CNS) is limited [31,32], (2) enzyme is rapidly cleared from blood circulation (short half-lives), (3) ERT has immunological problem [33], and (4) ERT is very expensive [31] (Table 1). Only a fraction of the enzyme is delivered into bone and cartilage lesions since the mannose 6-phosphate residues on lysosomal enzymes bind to mannose 6-phosphate receptors (M6PRs) in visceral organs such as liver, spleen, and kidney. The enzymes injected are rapidly removed from the circulation [34]. Enzyme delivery to bone and cartilage is decreased compared to visceral organs due to relatively reduced perfusion to the skeletal system. Long-term therapy of ERT does not improve bone and cartilage lesions in patients with MPS I [23].

### 2.2. ERT for Morquio A

In 2014, the US Food and Drug Administration and the European Medicines Agency approved recombinant human GALNS (elosulfase alfa, Vimizim®) as conventional ERT for Morquio A patients. Prior to approval, a phase I/II clinical trial examined 20 patients in an open-label, dose escalation trial. A total of 176 patients with Morquio A participated in a phase III clinical trial. This clinical trial was a randomized, double-blind, placebo-controlled study and consisted of two consecutive studies (MOR-004 and MOR-005) [14,15,35]. Patients were excluded from the study due to safety concerns if patients were younger than 5 years, could not walk more than 30 m in a 6-minute walk test (6MWT), patients who had undergone surgical interventions within 3 months prior to trial entry or had planned surgery during the clinical trial period, and patients who had disease or conditions such as cervical

spine instability, spinal cord compression, and severe cardiac disease. Thus, patients most likely to respond well to therapy (young patients) and more severely affected patients were excluded from the study. The primary efficacy end point was the 6MWT. After 24 weeks, patients dosed weekly by ERT (but not those dosed every other week) walked significantly further than placebo controls in the 6MWT. However, there was no further improvement in this treated group beyond 36 weeks. Furthermore, at the end of the first phase of the study, patients in the control arm of the study who were given the treatment for 48 weeks showed no improvement in the 6MWT. Thus, although the primary outcome of the clinical trial was successful, improvements were modest and limited to an improvement in the 6MWT. A secondary end point, the 3-minute stair climbing test, showed no significant improvement in the treatment arms of the study. Urinary KS levels were significantly reduced in the treated groups, but decreases in urinary KS did not correlate with therapeutic efficacy.

Outcomes of the 6MWT vary depending on the type of chronic illnesses under study [36], so experts recommend additional clinical outcome measurements to interpret the clinical significance of any improvements in the 6MWT for specific chronic disease populations. Thus, additional measurements of therapeutic efficacy are needed to better evaluate efficacy of treatments for Morquio A [14]. We have evaluated the effects of ERT treatment on ADL and surgical intervention in patients with Morquio A [37]. ADL scores for ERT patients under 10 years of age (2.5 years follow-up on average) were similar to those of age-matched controls, but for older patients, ADL scores were lower than age-matched controls. Surgical frequency did not decrease after ERT treatment and was not decreased compared to untreated patients [37]. In the UK, a ‘managed access’ program has been formulated in December 2015, in which a drug is made available for a limited period of time (e.g. for 5 years) often at a discounted price, to allow further evidence to be gathered on its effectiveness while ensuring that patients receive access to the drug. Through this, it can be monitored how well the medicine has worked in practice before future funding decisions are taken [38]. In The Netherlands, it was initially reimbursed, but reimbursement was stopped when the authorities decided that the data provided were limited to a suboptimal short-term outcome in a heterogeneous population, showing a small effect that was not clinically relevant.

To date, there are no reports on the effect of ERT on bone and cartilage lesions and resolution of bone and cartilage lesions, a critical issue for patients with Morquio A. We showed that chondrocytes and extracellular matrix (ECM) derived from Morquio A patients, who had received ERT for 6–30 months, showed no decrease of vacuoles in bone pathology [16,17]. These pathological findings are consistent with the fact that frequency of need for orthopedic surgical interventions has not been reduced by ERT (average duration of ERT: 2.5 ± 1.0 years) [37]. Longer-term assessment of conventional ERT is required to determine whether it can improve bone and cartilage lesions.

The GALNS enzyme tagged with acidic amino acid residues (bone-targeting enzyme) had a markedly prolonged clearance from the circulation, leading to 10–20 times higher concentration of the enzyme activity in blood than those of the native enzyme in an MPS IVA mouse model [39]. Bone-targeting ERT provides more impact on the bone lesions in a Morquio A mouse model [39]. Targeting of the enzyme to bone and/or treating at the

newborn stage presents more improvements in the clinical manifestations and pathological bone lesions in mouse models. It is critical to evaluate the therapeutic effect to bone and joint lesions by using molecules with increased tropism toward those tissues.

## 3. HSCT

### 3.1. HSCT for MPS

In 1981, Hobbs et al. first reported bone marrow transplantation in a 1-year-old boy with Hurler syndrome (MPS I) and showed that deterioration in the child's development had been arrested with recovery of enzyme activity and a reduction in GAGs [40]. To date, HSCT has been performed in approximately 1000 patients with MPS I, MPS II, MPS VI, and MPS VII [12,41–47]. The secreted lysosomal enzyme from bone-marrow-derived donor cells can systemically circulate in blood, be delivered into various tissues, and degrade accumulated GAG. HSCT still has limited effect on bone and cartilage lesions due to the limited blood flow and dense matrix in these tissues that impairs cell penetration. Clinical outcome of HSCT depends on (1) age and disease stage, (2) type of MPS, (3) type of donor (related or unrelated, bone marrow, or umbilical cord blood), and (4) clinical severity of MPS.

In patients with Hurler disease (MPS I), HSCT clinically improves psychomotor performance, neurocognitive performance, hearing loss, joint mobility, and growth. Early treatment with HSCT is the gold standard for MPS I patients under 2 years of age, and impairment of mental development is substantially reduced when compared with patients more than 2 years of age. Bone pathology is also substantially improved (Figure 1).

The efficacy of HSCT for MPS II reported by Tanaka et al. (2012), Patel et al. (2014), Shimada et al. (2014), and Tanjuakio et al. (2015) has been confirmed with improvements of magnetic resonance imaging (MRI) findings, growth, GAG levels, and ADL. HSCT has shown a better improvement in MRI findings, GAG levels, and ADL [41,44,48]. To date, approximately 60 patients with MPS II have received HSCT in Japan, leading to improvements that depend on age at transplantation, clinical severity, and CNS involvement [41,44]. HSCT for MPS II has been approved and accepted as a standard of care in Japan. HSCT also delays the progression of disease in MPS VI and MPS VII patients [12,16,45,49]. However, preexisting skeletal phenotypes are not improved by HSCT indicating that bone abnormalities present at the time of transplant are irreversible. Patients may need to undergo orthopedic corrective operation for skeletal abnormalities after HSCT, even though skeletal histopathology of surgical remnants from a MPS I patient 10 years after HSCT showed that chondrocytes were normal sized without excessive vacuoles [50]. There are critical benefits of HSCT over conventional ERT for patients with MPS. HSCT provides continuous enzyme expression from donor cells and this continuous effect requires a single treatment. Thus, HSCT is less expensive than ERT. However, there are disadvantages of HSCT: (1) high mortality risk, (2) age limitation, (3) limitation by health condition, and (4) limitation by medical facility [16] (Table 1). The major mortality risks are due to development of acute graft versus host disease (GVHD), development of infectious diseases due to use of immunosuppressants, and organopathy associated with chemotherapy and radiation therapy. Recently, progress of medical technology and accumulation of HSCT cases have contributed to improvements in treatment regimens and a substantial reduction in

mortality rates for patients with MPS [51]. Recent reports indicate that overall survival is 95.2% in a well-trained facility.

### 3.2. HSCT for Morquio A

We have examined four cases of Morquio A (three with a severe form and one with an attenuated form) who had HSCT and have followed these patients for at least 10 years [18,19]. HSCT was conducted between 4 and 15 years of age (mean: 10.5 years), and their present ages range between 25 and 36 years (mean: 19 years posttreatment). All HSCT cases achieved a successful full engraftment without a serious GVHD. After undergoing HSCT, GALNS enzyme activity of recipient's lymphocytes in all cases reached the donor's level. A fifth patient who underwent bone marrow transplantation at 12 years of age with cells from his elder brother did not obtain successful engraftment [52]. At 20 years, he died of respiratory complication due to tracheal obstruction during postsurgical procedure. The death of the patient was not related to complications of HSCT. Tracheal obstruction is one of the critical issues that leads to high mortality and morbidity in Morquio A patients. For the patient who underwent HSCT at 15 years of age, pulmonary function parameters showed a great improvement after receiving HSCT. Vital capacity (VC) was elevated from 1.08 to 1.31 (L), %VC from 43 to 48.2 (%), peak expiratory flow from 2.03 to 2.36 (L/S), and one second forced expiratory volume ($FEV_{1.0}$) from 1.08 to 1.12 (L) 3 years after HSCT [18]. This improvement has been maintained 11 years post-HSCT. None of the four HSCT patients have tracheal obstruction or severe respiratory problem. These results indicate that HSCT prevents development of tracheal obstruction or severe respiratory issues for Morquio A patients.

Total ADL scores in Morquio A patients treated with HSCT were better than in age-matched untreated patients. Total average ADL score of the four HSCT treated patients was 48.3 (maximum score is 60, higher scores are better), while the score for untreated patients over 20 years of age is 38.5 ($n = 16$). The patient who had been treated at the earliest age (4) had the highest ADL score of 59. There was a clear improvement in walking, stair climbing, endurance, and hand movement in all four HSCT cases. None of these treated patients developed serious heart valve disease [19].

A patient with a severe type of Morquio A showed an increase in bone mineral density (BMD) at L2–L4 from 0.372 $g/cm^2$ before HSCT to 0.548 $g/cm^2$ 1 year after treatment and $0.48 \pm 0.054$ $g/cm^2$ 9 years later.

Morquio A patients often need multiple surgical interventions such as spinal cervical fusion/decompression, leg osteotomy, and hip correction or replacement during their lives. Three patients have had no surgical interventions since HSCT. One patient underwent bilateral osteotomies at 16 years of age, 1 year after HSCT but has not needed spinal cord decompression/fusion. While untreated Morquio A patients need to use wheelchairs or move by crawling by the time they become teenagers [7], all four HSCT patients currently aged 25, 36, 31, and 26 live and walk independently. Thus, HSCT for patients with Morquio A reduces the number of surgical interventions needed, and these clinical outcomes indicate that HSCT can prevent and slow the progression of skeletal dysplasia [19].

However, HSCT has a limited impact on overall growth in patients with a severe form of Morquio A. Short stature with a short trunk is a characteristic of patients with Morquio A, and growth typically stops at 4–8 years of age. The final height of the patient treated with HSCT at aged 4 was only 9 cm above the average final height of Japanese female Morquio A patients; 104 cm, and her body weight was 26 kg at 20 years of age [19].

Accordingly, HSCT appears to have a limited effect on preexisting skeletal abnormalities in Morquio A patients. However, if HSCT could be performed during the first months of life, it should prevent skeletal dysplasia in patients with Morquio A since bone development appears nearly normal during the neonatal period and even excessive growth is observed in some patients [7,9,16,17,19,41].

The study of long-term outcomes after HSCT in these four Morquio A patients demonstrates that HSCT can increase the enzyme activity of GALNS, reducing the frequency of surgical intervention, reducing occurrence of heart valve disease, and improving pulmonary function, ADL, and BMD. This suggests that HSCT is a useful treatment option for patients with Morquio A. We need to accumulate more cases with HSCT and evaluate the long-term clinical outcomes of Morquio A patients.

## 4. Gene therapy

Gene therapy for MPS is not yet available in clinical practice; however, clinical trials for some types of MPS are under way in the United States and some European countries [20,53]. Phases I/II clinical trials for Sanfilippo A syndrome (MPS IIIA) are ongoing [54], and trials for MPS I and II are scheduled. Gene therapy for MPS is deemed as regenerative medicine and expected to be a one-time treatment since the active enzyme is secreted from transduced cells and circulated continuously as observed in HSCT (Table 1). There are two major methods of gene therapy: (1) direct injection of viral vector intravenously or locally and gene delivery into human somatic cells (*in vivo* gene therapy) and (2) gene insertion in somatic cells derived from the recipient outside the body and transplantation back to the patients again (*ex vivo* gene therapy). Gene therapy studies for MPS have been reported using mice and large animal models. For *in vivo* gene therapy, the gene of the lysosomal enzyme is inserted into viral vectors such as retroviral, lentiviral, adenoviral, and adeno-associated virus (AAV)-based vectors, and the vectors are administered into model animals. For in *ex vivo* gene therapy, retroviral vectors are mainly used to transduce lysosomal genes into various cells such as bone marrow [55–60], fibroblast [61–63], and myoblast cells [64,65]. These transduced cells are cultured and then transplanted into recipients with a standard procedure of bone marrow transplantation in preclinical trials. Although gene therapy in an adult MPS mouse model showed pathological improvement in organs such as liver, spleen, and kidney, there was no effect on skeletal and brain lesions. It is likely that penetration of gene vectors into these lesions is limited in adulthood. The immune response may also affect therapeutic efficacy in mature mice. Early treatment in the neonatal period could prevent generation of immune reactions. Hartung et al. showed that intravenous administration of AAV vector carrying human a-L-iduronidase gene into neonatal MPS I mice improved bone and CNS lesions [66]. Skeletal lesions in MPS VII mice also improved in similar systemic injections of neonatal mice using an adenovirus vector carrying the gene

for β-glucuronidase [67,68]. Therefore, early gene therapy will likely be important to effectively prevent irreversible pathological lesions in MPS patients.

Currently, several preclinical trials of gene therapy for Morquio A are under way. A retrovirus vector expressing GALNS enzyme was used in the first study of gene therapy for Morquio A [69]. GALNS activity levels in Morquio A skin fibroblast cells were substantially increased compared with those in non-transduced cells, and GAG accumulation was reduced in transduced cells. This study indicated that human GALNS may be expressed either systemically or locally by *ex vivo* gene therapy. However, retroviral vectors need to be used with caution as they can have serious adverse oncogenic effects [70]. Thus, the evaluation of different gene therapy vectors is required.

Gene expression mediated by AAV is maintained long term, and AAV is relatively safe compared with other vectors since the gene is inserted into specific locations in chromosomes. AAV vectors have been used in several preclinical and clinical trials on lysosomal diseases and provided clinical improvements [71,72]. Gutiérrez et al. showed that an AAV vector carrying the GALNS gene with the promoter for cytomegalovirus (CMV) increased GALNS activity 48 h post-transduction in HEK293 cells and skin Morquio A fibroblast cells [73]. AAV vectors using the promoters of elongation factor 1α (EF1) or α1-antitrypsin (AAT) were also developed since expression by the CMV promoter was not maintained and immune reactions may be a problem *in vivo*. The EF1 and AAT promoters provide the same GALNS activity levels as observed with the CMV promoter in human Morquio A fibroblast and murine Morquio A chondrocytes [74,75]. Furthermore, Fraldi et al. investigated the combination effects of expression of GALNS with sulfatase modifying factor 1 (SUMF1) on enzyme activity in Morquio A cells since it was reported that cotransduction of SUMF1 enhanced GALNS activity in cells derived from patients with lysosomal disease [76]. GALNS activity was significantly induced by co-expression of SUMF1 in human Morquio A fibroblast and murine Morquio A chondrocyte [74,75].

The unique skeletal manifestation of Morquio A requires an efficient method of gene delivery to bone and cartilage lesions. We have designed a method of bone targeting gene therapy that integrates multiple copies of a short acidic amino acid peptide into the AAV2 vector capsid. A sequence encoding eight aspartic acidic residues (D8) was inserted into this vector just behind the initial codon of the viral protein 2, leading to expression of multiple copies of the D8 peptide on the capsid surface. This vector capsid was efficiently concentrated in bone by binding to hydroxyapatite (HA). On release from HA, it was transduced into adjacent bone and cartilage cells. After intravenous administration of this modified vector capsid into a Morquio A model mouse, expression of GALNS in bone was significantly elevated when compared with enzyme levels in bone of mice transduced with the unmodified vector [9]. Therefore, bone targeting gene therapy is a potential option to improve the bone and cartilage lesions of patients with Morquio A in the future.

## 5. Surgical intervention

### 5.1. Orthopedic surgery for Morquio A

Morquio A syndrome is characterized by excess accumulation of KS and C6S in bone and cartilage. KS and C6S are synthesized mainly in cartilage cells [77–79], and deficiency of GALNS causes accumulation of undigested GAGs in lysosomes of cartilage cells. We have reported that an autopsied case with Morquio A revealed infiltration of foam cells in multiple organs including bone and cartilage, leading to local inflammation [52]. These findings indicate that accumulation of GAG and successive chronic inflammation lead to the development of skeletal deformity in patients with Morquio A. Severe skeletal deformity with an imbalance of growth causes a lower ADL and is a life-threatening problem. Most patients with Morquio A appear normal at birth and may not be diagnosed until later in life. Patients with a severe form often have kyphoscoliosis and thoracic deformity in the first year. Over 70% of Morquio A patients have skeletal symptoms such as pectus carinatum, laxity of joints, kyphoscoliosis, and genu valgum by the age of five [7,80]. Currently, there is no effective therapy for established skeletal abnormality in patients with Morquio A. Thus, patients often require multiple orthopedic surgeries in the upper cervical spine and lower extremities in their first decade of life [7]. Cervical spine instability, a distorted airway, and heart valvular disease make anesthetic care more risky during these procedures and can lead to spinal cord infarction, paraplegia, and mortality [7–9,13,80,81]. Evaluation of these risk factors before surgical intervention and perioperative anesthetic care of patients is required to prevent complications during and after anesthesia. Management of the difficult airway in patients with Morquio A is a challenge. Therefore, anesthesia in Morquio A patients should be performed cooperatively by well-trained multidisciplinary team with an anesthesiologist with experience in caring for patients with difficult airways.

### 5.2. Cervical surgery

Odontoid dysplasia, ligamentous laxity, and incomplete ossification of the anterior and posterior atlas are common among children with Morquio A. These problems can cause instability of the neck and upper spinal cord compression, leading to quadriplegia, chronic myelopathy, and sudden death due to respiratory restriction [7–9,13,82,83]. In general, prophylactic treatment of atlantoaxial instability is not recommended [84]. Upper cervical spine decompression/fusion improves spinal cord compression in Morquio A patients. Although radiography, computed tomography (CT), and MRI have been used to diagnose and monitor spinal problems; MRI is currently the most useful imaging tool for evaluating the severity of spinal cord compression and stenosis [85] (Figure 2). Thus, early diagnosis and management of cervical spine compression, instability, and spinal stenosis are required to prevent myelopathy and other complications [86,87]. However, in a long-term follow-up study, distal junctional instability is a major issue after surgical intervention in patients with Morquio A, and an additional surgery in the lower cervico-thoracic spine is required in 40% of patients [88].

### 5.3. Low extremity surgery

Progressive coxa valga, genu valgum, and ankle valgus are main features of the lower extremity in patients with Morquio A [89]. These deformities are observed in Morquio A

children, and surgical intervention is often required to improve function [90]. Hips appear either normal or partially dislocated as early as the second year of life in severe type of Morquio A patients. Morquio A children have small capital femoral epiphyses. Epiphyses are progressively decreased with growth and finally lost in adulthood. Hip subluxation and associated pain often force Morquio A patients to become wheelchair bound in teenage years if surgical interventions have not been performed [12]. Hip reconstructive surgery such as shelf acetabuloplasty and varus derotation osteotomy is needed to treat and ameliorate hip pain and restriction of movement; however, hip reconstructive surgery is a challenge in patients with Morquio A due to a deformed acetabulum [91]. It was reported that a recurrent hip subluxation happens in Morquio A patients after shelf acetabuloplasty and varus derotation osteotomy [90]. Hip replacement surgery may be required in adult patients with Morquio A, who have severe arthritis and pain [9,12].

Patients with Morquio A also have lower extremity abnormalities such as knee flexion, genu valgum, and external tibial torsion, and need surgical procedures to improve function [9,12,18]. Knee deformity most commonly happens in children with Morquio A at 3 years of age. Guided growth (8-plate hemiepiphysiodesis) may be a useful option to correct genu valgum in children if they have enough growth plate [90,92]. Patients who have limited remaining growth or severe genu valgum require osteotomy. This osteotomy needs to separate the femur and tibial bones and reconstruct the knee. However, it takes a long time to correct genu valgum if the deformity is severe, and it is difficult to return to their preoperative function level [91]. Thus, genu valgum-related treatment should be initiated before progression of the deformity and patients may need surgery as young as 4 years of age [91]. Repeated surgical procedures for knee deformities are often needed in patients with Morquio A as they grow.

### 5.4. Tracheal surgery

**5.4.1. Tracheal obstruction—**Tracheal obstruction can lead to death due to sleep apnea and related complications. Tracheal obstruction is caused by multiple factors: (1) disproportionate development between neck, brachiocephalic artery, chest cavity, and trachea; (2) accumulation of GAGs in the airway; and (3) a severe pectus carinatum narrowing a thoracic cavity and a thoracic inlet [10]. The etiology of tracheal impingement appears to be due to a combination of the narrow thoracic inlet crowding structures and the disproportionate growth between trachea, brachiocephalic artery, cervical spine, and rib cage.

Although tracheostomy is often used to improve airway obstruction in patients with Morquio A, perioperative upper airway management and anesthetic management during surgical procedure is very difficult in severe form of patients due to a short neck, instability of cervical vertebrae, and a twisted and redundant trachea [52,80,86,93–96]. Imaging techniques such as CT, X-ray, and MRI are often used to help diagnosis for cervical spinal cord injury in Morquio A patients. However, tracheal obstruction is often overlooked during surgery.

We performed a retrospective study on tracheal obstruction in Morquio A patients [10]. We investigated trachea obstruction in a total of 28 patients with Morquio A. A total of 19

patients (67.8%) had symptoms which were associated with at least 25% tracheal narrowing by MRI images of the cervical spine. Eight of these patients (28.6%) showed severe narrowing (75% stenosis of the trachea) (Figure 3). Narrowing of the trachea has been seen in a child as early as 2 years of age, and tracheal obstruction increased with age in Morquio A patients. The tracheal obstruction severity score in patients over 15 years of age was almost twice as high as that of patients in the 10–15 age range. Compression of the trachea by the brachiocephalic artery is one of the important contributors to airway obstruction, which is associated with cough, pulmonary infections, expiratory strider, and apnea [96]. Compression of the trachea by the brachiocephalic artery was seen in 15 of the 19 patients with tracheal obstruction. Excessive connective tissue is also involved in compression of the trachea. Most patients had thickening of the tracheal wall due to accumulation of GAG and tissue inflammation, contributing to airway narrowing [52].

This retrospective study indicates that tracheal obstruction is common among these patients and requires careful assessment of the airway with imaging including CT angiogram scan of the chest and broncoscopy which provide optimal evaluation of the trachea and surrounding structures. Management guidelines for tracheal obstruction in Morquio patients are much needed in order to recognize those individuals with airway obstruction due to tracheal compromise and to reduce the mortality rate in patients with Morquio A. As of now, ERT or other therapies have not yet proven to improve tracheal obstruction for Morquio A patients. Thus, at present, surgical operation is the only way to improve preexisting airway obstructions. Recently, we have successfully utilized a new surgical intervention to relieve severe tracheal obstruction in four patients.

## 6. Case report

A 16-year-old male patient was diagnosed with Morquio A at 18 months of age on the basis of kyphosis and enzyme activity assay and had the homozygous genotype for p.R386C/p.R386C causing a severe phenotype. KS levels in blood and urine at age 4 showed a marked elevation with 1112 ng/ml and 2.6 mg/g creatinine, respectively. He had already received orthopedic surgical procedures to stabilize his cervical spine and lower extremity. The patient underwent occipt to C2 fusion at 3 years of age and occipt to C4 fusion at 12 years of age with progression of cervical cord compression. The patient participated in the clinical trial of ERT at 14 years of age. He exhibited sleep apnea and intermittent snoring during a sleep test at 12 years of age. His deviated trachea was also found during intubation at the last elective orthopedic surgery. The patient had breathing difficulty and started to use bilevel positive airway pressure ventilation at night. During a spirometry test at 16 years of age, he was diagnosed with severe obstructive lung disease. CT scan and MRI demonstrated a compression of the anterior trachea by the brachiocephalic artery. Although tracheostomy has been used to bypass airway obstruction in Morquio A patients, his parents declined its use due to concerns about lifestyle and challenges associated with maintenance. A surgical procedure was performed which included reimplantation of the brachiocephalic artery to relieve obstruction of the proximal trachea induced by vascular impingement, followed by resection of redundant trachea with end-to-end anastomosis [22]. Postoperatively, his respiratory difficulty was markedly improved and ADL score enhanced. His FEV1/FVC ratio of spirometry measurements increased from 40% to 86%. Abundant GAG loaded

vacuoles were found in tracheal chondrocytes by toluidine blue staining, despite 2.5 years of ERT. These chondrocytes were also hypercellular and ballooned, and the column structure was disorganized (Figure 4).

This was the first Morquio A case suffering from severe tracheal obstruction to be rescued successfully by surgical intervention without tracheostomy. Since the original report, three additional cases have been successfully treated using this surgical operation. All patients recovered from surgery without any complications and their pulmonary functions were markedly improved. Additional experience will be required to evaluate the procedures of this new intervention and its consequences. This new surgical operation may be the best option to improve fatal tracheal obstruction with Morquio A patients. Current approved ERT for Morquio A does not seem to prevent tracheal obstruction, so such surgical interventions are likely to be necessary until more permanent cures are found.

## 7. Expert opinion

Conventional ERT and HSCT are currently available in clinical practice for patients with Morquio A (Figure 5). These therapies show a partial improvement in symptoms and ADL, but they have a limited effect on established bone and cartilage lesions. While our studies indicate that HSCT can prevent and slow the advancing of skeletal dysplasia in patients with Morquio A compared with that of ERT [18,19], more HSCT cases for Morquio A are needed to assess the transplant process and its consequences. Guidelines for optimal timing of this treatment are also needed. Gene therapy is also expected to be a one-time permanent treatment by maintaining enzyme activity continuously. Opitmization of type of vector, route of administration, and adverse effects are yet to be determined (Table 1). Surgical intervention is often required to improve quality of life in patients with Morquio A, and currently, it is important that surgical intervention must be combined with ERT or HSCT. A newly developed surgical intervention for tracheal obstruction is currently the best option to improve a severe narrowing trachea and to reduce the high mortality rate caused by this complication of Morquio A. A well-trained clinical team and facility are required to reduce the risk of respiratory failure in Morquio A patients.

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## Article highlights

- Description of clinical effect and limitations of current therapies for Morquio A.
- Limited improvement of ERT and HSCT in bone.
- Cases with severe tracheal obstruction by a new tracheal surgery.
- Gene therapy as a new therapeutic option for Morquio A.

This box summarizes key points contained in the article.

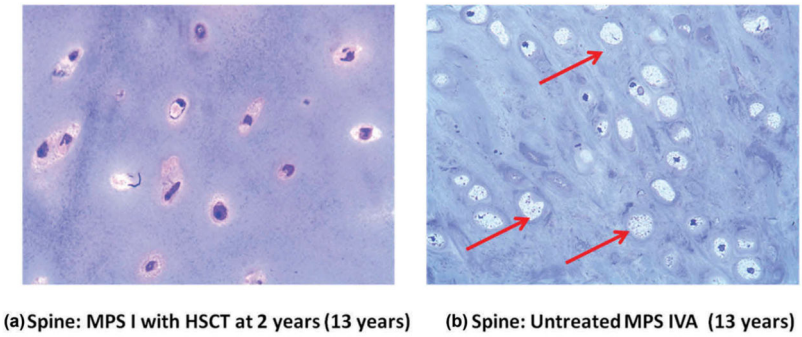


**Figure 1.**

Bone pathology of the spine in a 13-year-old patient with MPS I after HSCT and a 13-year-old untreated patient with MPS IVA. Left panel (a); Chondrocytes in an MPS I patient treated with HSCT, right panel (b); chondrocyte in an untreated patient with MPSIVA. Arrows show chondrocytes filled with vacuoles. HSCT, hematopoietic stem cell transplantation.

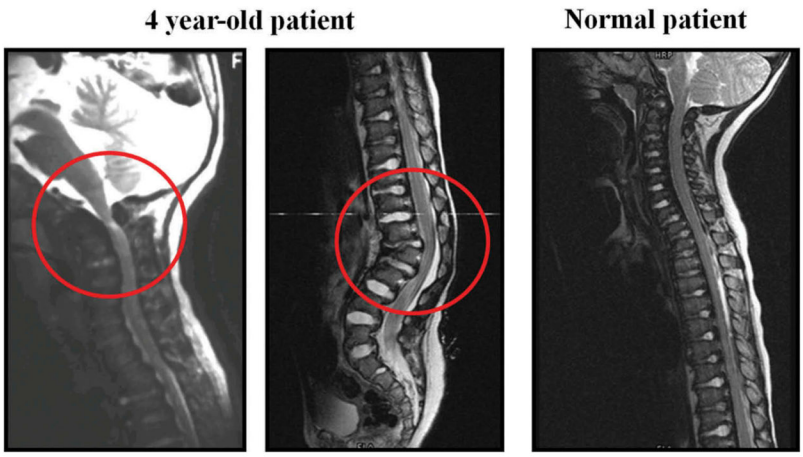


**Figure 2.**

MRI of cervical spine in a 4-year-old patient with Morquio A. The red circles show the spinal cord compression. A baseline study of the upper cervical anatomy is recommended no later than 2 years or at diagnosis using flexion/extension X-ray films. If patients have a severe pain or pain associated with weakness of strength or tremors (or clonus) in the arms or legs occur, the patient should have tests of the neck to evaluate for cervical vertebral subluxation and spinal cord compression (adapted from Educational CD for Morquio and permitted by Carol Ann Foundation). Full color available online.

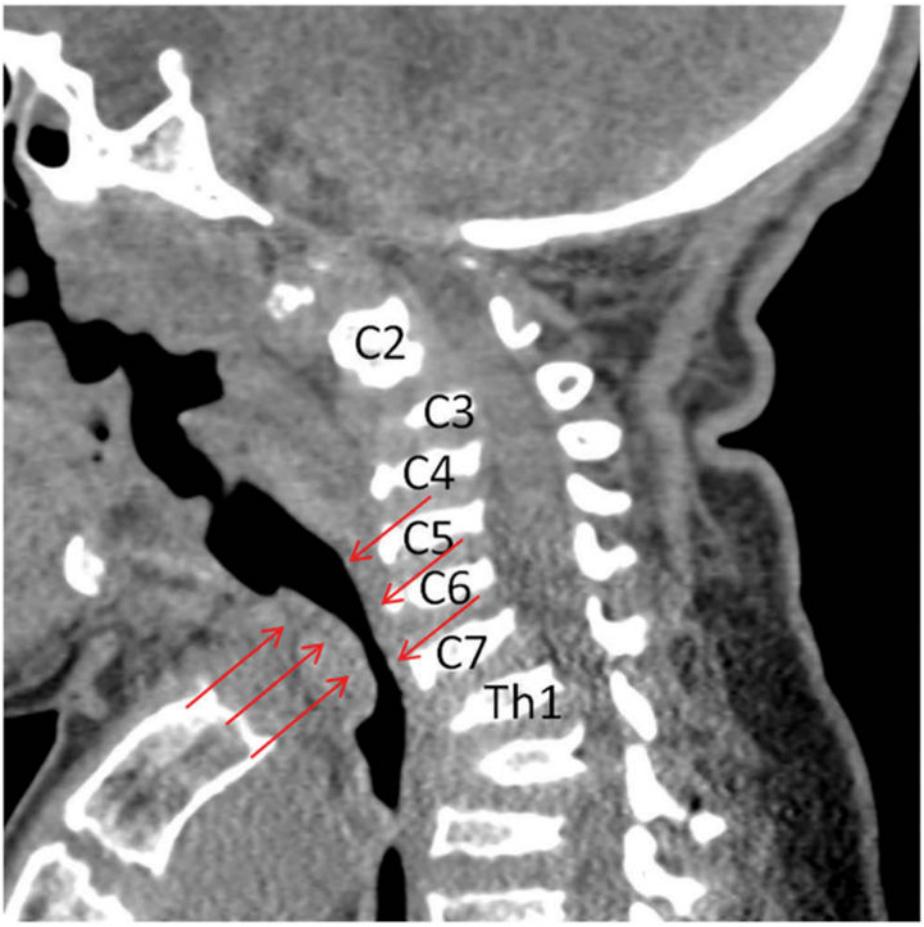


**Figure 3.**
CT of tracheal obstruction in a 17-year-old patient with Morquio A. CT shows that a 17-year-old patient has over 75% of tracheal obstruction (severe narrowing case). This patient underwent corrective tracheal surgery at the age of 23 years and recovered from tracheal obstruction. Trachea is compressed and twisted with mass effect.

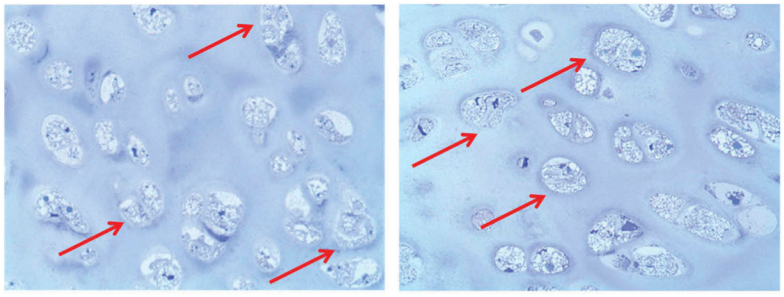


**Figure 4.**

Chondrocytes in trachea (light microscopy). Trachea with toluidine blue staining shows enlarged vacuolated chondrocytes. Arrows show chondrocytes filled with vacuoles. Left panel, hyaline chondrocytes (40x); right panel, hyaline chondrocytes (40x). Full color available online.

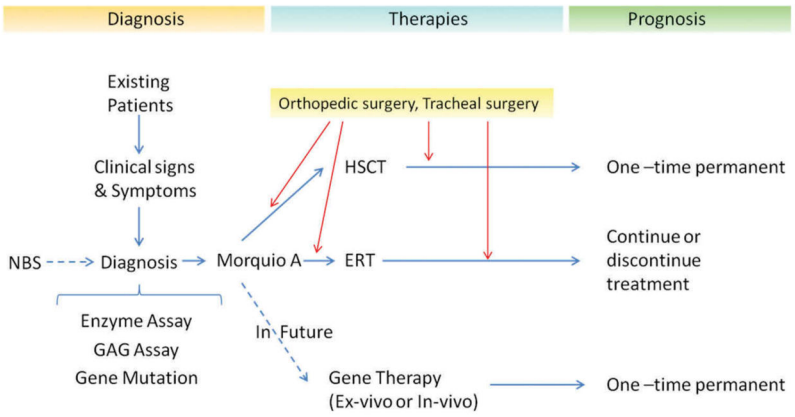


**Figure 5.**

Current and future management guideline of Morquio A syndrome.

Abbreviation: NBS, newborn screening; GAG, glycosaminoglycan; ERT, enzyme replacement therapy; HSCT, hematopoietic stem cell therapy.

**Table 1**

Comparison of advantage and disadvantage of ERT, HSCT, and gene therapy for Morquio A.

| | Advantages | Disadvantages |
|---|---|---|
| ERT ($400,000 per year per 25 kg) * | Low risk of mortality and morbidity | Very expensive |
| | No limitation of age | Continuous weekly treatment |
| | No limitation of health condition | Short half-life of enzyme |
| | No specialized medical facility required | |
| HSCT (approximately $100,000) * | Lowest cost | Risk of mortality |
| | One-time permanent treatment | Limitation of age |
| | Continuous activity of enzyme | Limitation of health condition |
| | More effect in bone pathology | Specialized medical facility required GVHD availability of a donor |
| | Advantages | Problems to overcome |
| Gene therapy | One-time permanent treatment | Vector selection needs to be determined |
| | Continuous activity of enzyme | Administration route not determined |
| | Lower cost than ERT | Adverse effects: off-target effect |
| | Efficacy not proven | |
| | Does not require donor | Unknown effect of long-term expression |
| | No age limitation | |

* Cost of HSCT or ERT in Japan.

ERT, enzyme replacement therapy; GVHD, graft versus host disease; HSCT, hematopoietic stem cell therapy.