Pharmacotherapeutical Review

Laronidase (Aldurazyme®)

Indication:

Mucopolysaccharidose type I (MPS I)

Programma

Dure Geneesmiddelen

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Contents

Abbreviations 3

Summary 4

1. Introduction 7

1.1 Laronidase 7

1.2.A Registered indications for laronidase 7

1.2.B Indications for which registration is requested 7

1.3 Current reimbursement of laronidase 7

1.4 Signs and symptoms for which laronidase is prescribed 7

1.5 Pathophysiology of MPS I 8

1.6 Prevalence of the disorder 8

1.7 Severity of MPS I 8

1.8 Treatment of MPS I 9

1.9 Proposed indication of laronidase in the treatment of MPS I 9

2. Methods 12

2.1 Alternative treatment option(s) 12

2.2 Review of the literature 12

2.3 Relevant clinical trials 12

3. Therapeutic value 17

3.1 Beneficial effects of Laronidase 17

3.1.1 Outcome parameters 17

3.1.2 Motivation for excluding outcome parameters 17

3.1.3 Efficacy of Laronidase on relevant outcome parameters 18

3.2 Adverse effects of Laronidase 22

3.3 Experience with Laronidase 24

3.4 Applicability 25

3.5 Ease of use 25

4. Conclusions 26

References 28

Addenda 29

Abbreviations

6-MWT	6-Minute Walk Test
AHI	Apnoea-Hypopnoea Index
CFH	Commissie Farmaceutische Hulp
CNS	Central Nervous System
DQ	Developmental Quotient
EMA	European Medicines Agency
ERT	Enzyme Replacement Therapy
FDA	Food and Drug Administration
FVC	Forced Vital Capacity
GAG	Glycosaminoglycan
HSCT	Hematopoietic Stem Cell Transplantation
IAR	Infusion-associated reaction
IQ	Intellectual Quotient
MPS I	Mucopolysaccharidosis type I
RCT	Randomized Controlled Trial
ROM	Range of Motion

Samenvatting

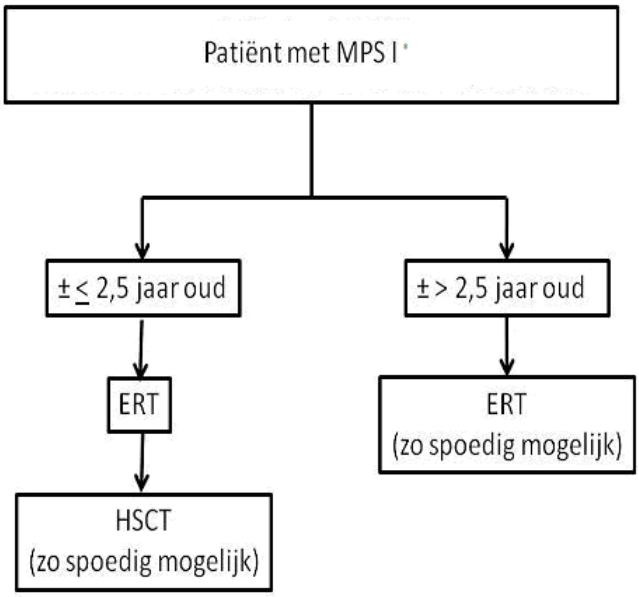
Claim van de fabrikant

Laronidase (Genzyme Corp.) is geïndiceerd voor de lange termijn behandeling van de niet-neurologische verschijnselen van patiënten met een bevestigde diagnose van de ziekte Mucopolysaccharidose type I (MPS I).

Inleiding

Laronidase is een recombinante vorm van humaan α-L-iduronidase. Laronidase wordt intraveneus toegediend (enzymvervangingstherapie, ERT) in een dosering van 100 IU/kg/week en is geïndiceerd voor de lange termijn behandeling van de niet-neurologische verschijnselen van patiënten met de ziekte MPS I.

MPS I wordt veroorzaakt door deficiëntie van het enzym α-L-iduronidase, een lysosomaal hydrolase dat nodig is om de glycosaminoglycanen (GAGs) heparan- en dermatansulfaat in het lichaam af te breken. Door stapeling van GAGs ontstaat uitgebreide en progressieve cel- en orgaanschade. MPS I kent een breed fenotypisch spectrum, variërend van relatief mild (ziekte van Scheie) tot zeer ernstig (ziekte van Hurler). Behandeling met laronidase heeft tot doel de capaciteit voor het afbreken van GAGs te vergroten en aldus verdere stapeling van GAGs te voorkomen. Omdat laronidase de bloed-hersenbarrière niet kan passeren, heeft laronidase geen effect op neurologische schade veroorzaakt door deze ziekte.



Bovenstaande figuur geeft de plaats van behandeling met laronidase (ERT) weer in het behandelschema van patiënten met MPS I. Dit behandelschema is gebaseerd op internationale consensus (zie pagina 10-12). Deze beslisboom is indicatief; per patiënt dient door de expertisecentra een individuele afweging gemaakt te worden.

* Diagnose gesteld op basis van deficiënte activiteit van α-L-iduronidase en/of mutatie-analyse.

Methoden

Behalve HSCT voor patiënten met MPS I die op grond van klinische verschijnselen al op zeer jonge leeftijd zijn gediagnosticeerd (de ziekte van Hurler), is er op dit moment geen andere oorzakelijke behandeling voor de ziekte MPS I beschikbaar.

Laronidase is geregistreerd voor de langdurige behandeling van de niet-neurologische verschijnselen van patiënten met MPS I met als doel de symptomen van de ziekte te verminderen of te stabiliseren. Het effect van laronidase kan alleen vergeleken worden met het natuurlijk beloop van de ziekte (altijd een progressieve multi-orgaan ziekte) of met placebo in randomized controlled trials (RCTs). In 2003 concludeerde de Commissie Farmaceutische Hulp (CFH) dat er op dat moment nog onvoldoende gegevens beschikbaar waren om tot een goed oordeel te komen over de therapeutische waarde van laronidase bij de behandeling van MPS I (CFH-rapport 03/15, 10 juli 2003). Voor beoordeling van therapeutische waarde baseerde de CFH zich op de fase I/II studie (1), op een deel van de resultaten van de fase I/II extensie studie, de fase III studie (2) en de eerste gegevens van de fase III extensie studie. Sinds 2003 zijn er meer data beschikbaar gekomen. De fase I/II extensie studie is gepubliceerd en geeft nu ook data over cardiale functie na langduriger behandeling (3). Daarnaast zij de langer termijn data van de fase III extensie studie beschikbaar gekomen en gepubliceerd (4). Hierin wordt de therapeutische waarde na 3.5 tot 4 jaar behandeling worden gepresenteerd (4). Tot slot zijn nog een aantal andere studies uitgevoerd om de therapeutische waarde van laronidase te bepalen, en zijn de gegevens van deze studies gepubliceerd (5,6).

De door ons op grond van methodologische overwegingen als meest relevant aangemerkte studies voor de bepaling van de therapeutische waarde van laronidase zijn de:

fase I/II–studie (10 patiënten) (1), fase III-studie (45 patiënten) (2), fase I/II- en III-extensiestudies (45 patiënten) (3,4), de studie naar het effect van laronidase bij patiënten jonger dan 5 jaar (20 patiënten) (5) en de dosering optimalisatie studie (de fase IV-studie; 33 patiënten) (6).

Daarnaast werd het therapeutisch effect van laronidase bij totaal 51 MPS I patiënten onderzocht in vijf open-label, single centre, prospectieve of retrospectieve case cohort studies en werd het effect en de veiligheid van behandeling met laronidase voorafgaand aan HSCT bestudeerd bij 59 MPS I patiënten met het ernstige (Hurler) fenotype.

Therapeutische waarde

Gunstige effecten:

De fase I/II-studie toonde aan dat intraveneuze toediening van laronidase veilig is en dat er na 52 weken behandeling sprake is van een significante afname in levervolume en tevens dat verbetering wordt waargenomen van groei, beweeglijkheid van gewrichten, hartfunctie en een afname van het optreden van slaapapneu's (1). Tijdens de 6-jaar durende follow-up studie worden deze bevindingen verder

bevestigd (3).

De fase III-studie toonde een statistisch significante toename in longfunctie en loopafstand afgelegd tijdens de 6-minuten looptest. Daarnaast wordt een significante afname beschreven van het levervolume, een afname in het optreden van slaapapneu's en een verbetering in beweeglijkheid van de gewrichten (2). De fase III-extensiestudie liet verdere verbeteringen in longfunctie, loopafstand, levervolume en beweeglijkheid van de gewrichten zien na een totale behandelduur van 4 jaar (4). Het effect van laronidase op patiënten jonger dan 5 jaar werd in een aparte studie geëvalueerd. Verbeteringen werden gerapporteerd in levergrootte, hartspierdikte en optreden van slaapapneu's na 52 weken van behandeling (5). Evaluatie van het effect van verschillende doseringen liet geen voordeel zien van andere doseringen dan die thans is geregistreerd en wordt toegepast (6).

Tot slot zijn er aanwijzingen dat er voor individuele patiënten een gunstig effect van laronidase optreedt, wanneer dit (kortdurend) toegediend wordt in de periode voorafgaand aan de HSCT (7-10).

De auteurs van dit review zijn van mening dat de therapeutische waarde van laronidase door bovengenoemd onderzoek voldoende is vastgesteld om het voorschrijven van dit middel in geselecteerde populaties van MPS I patiënten te rechtvaardigen. De 'level of evidence' van de relevante literatuur is A2 – C. Een juiste beoordeling van de kwaliteit en kwantiteit van het onderzoek is overigens alleen mogelijk indien hierbij zowel de extreme zeldzaamheid van de ziekte als de enorme fenotypische variatie van de ziekte worden meegenomen. Daarnaast hebben de twee projectleiders van het hier voorliggende review, (Prof.dr. Ans van der Ploeg, Rotterdam, en Prof.dr. Frits Wijburg, Amsterdam) beiden meer dan 11 jaar ervaring met het voorschrijven van laronidase bij patiënten met MPS I. Op grond van hun ervaring zijn zij van mening dat laronidase bij een geselecteerde groep patenten met MPS I voldoende therapeutische waarde heeft om te worden voorgeschreven (*expert opinion*, stand van de praktijk).

Ongunstige effecten:

Bijwerkingen bestaan met name uit koorts, braken, huiduitslag en urticaria. Over het algemeen zijn symptomen mild en van voorbijgaande aard. Premedicatie met antihistaminica en/of antipyretica lijkt bijwerkingen te kunnen voorkomen. Bijwerkingen doen zich voornamelijk voor aan het begin van de behandeling en nemen af naarmate patiënten langer behandeld worden. Ernstiger reacties, zoals anafylaxie en respiratoire insufficiëntie kunnen optreden, maar zijn zeer zeldzaam (1-6).

Nederlandse ervaring:

Omdat MPS I uiterst zeldzaam is, is de ervaring met laronidase in Nederland beperkt (addendum 1). Sinds het beschikbaar komen van laronidase als behandeling voor MPS I, zijn 47 patiënten met MPS I beoordeeld voor mogelijke behandeling met laronidase in de enige twee expertise centra van waaruit Laronidase in Nederland wordt voorgeschreven (ErasmusMC, Rotterdam, en AMC, Amsterdam). Op dit moment (december 2010) worden in Nederland 20 patiënten langdurig behandeld met laronidase. Dit is 5 patiënten minder dan het aantal patiënten dat in 2003 door de CFH geschat werd voor langdurige laronidase behandeling in aanmerking te komen (CFH-rapport 03/15, 10 juli 2003). De kosten voor laronidase gebruik in Nederland (gegevens december 2010) zijn dan ook nu per jaar ruim € 1, 5 miljoen lager dan aanvankelijk begroot door de CFH (CFH-rapport 03/15, 10 juli 2003). Daarnaast is bij 10 patiënten kortdurend (variërend van 1,5–8 maanden) laronidase gegeven voorafgaand aan een HSCT. Er zijn 4 patiënten die chronisch laronidase gebruikten overleden. Bij 1 patiënt die chronisch laronidase

gebruikte is de behandeling (op verzoek van de patiënt) gestaakt. Bij 11 MPS I patiënten is afgezien is van behandeling met laronidase. Van hen ondergingen 5 een HSCT, en zijn er 6 nooit met behandeling gestart.

Door de expertise centra wordt telkens voor iedere individuele patiënt een zorgvuldige afweging gemaakt of behandeling met laronidase geïndiceerd is. Hierbij wordt de ernst van de ziekte, de eventuele mogelijkheid voor HSCT voor patiënten met het ernstige (Hurler) phenotype, de te verwachten compliantie ten aanzien van enzymtherapie en de therapeutische waarde van laronidase zoals vastgesteld in wetenschappelijk onderzoek en ervaren door de experts (*expert opinion*), in de besluitvorming betrokken.

Toepasbaarheid:

De effectiviteit van laronidase is aangetoond bij patiënten met zeer uiteenlopende ernst van de ziekte (variërend van zeer ernstig tot mild) en zeer uiteenlopende leeftijden (variërend van zeer jong tot volwassen leeftijd) (1-6). Laronidase is dan ook toepasbaar voor alle MPS I patiënten, tenzij ernstige bijwerkingen optreden (zeldzaam). Laronidase is tevens geïndiceerd voor een deel van de MPS I patiënten die een HSCT zullen ondergaan, in de periode voorafgaand aan de HSCT, om de klinische conditie voorafgaand aan de procedure te verbeteren (7-10).

Gebruiksgemak:

Laronidase wordt eenmaal per week intraveneus toegediend. Toedieningduur is ongeveer 3-4 uur en varieert van 2 tot > 5 uur, inclusief voorbereidingstijd (addendum 2). Enzymbehandeling wordt opgestart in het ziekenhuis, waarna er gestreefd wordt naar verplaatsing van de behandeling naar de thuissituatie, onder verantwoordelijkheid van de voorschrijvende specialist in het expertisecentrum. Op die manier worden onnodig hoge kosten t.g.v. infusies in het ziekenhuis voorkomen en wordt de kwaliteit van leven van de patiënt bevorderd.

Conclusie

Laronidase is geregistreerd voor de langdurige behandeling van de niet-neurologische symptomen van MPS I patiënten en is effectief en veilig gebleken in de behandeling van meerdere symptomen van patiënten met uiteenlopende ernst van de ziekte en op verschillende leeftijden. Daarmee heeft laronidase bewezen van therapeutische waarde te zijn voor een geselecteerde groep patiënten met MPS I. Relatief kortdurende behandeling van geselecteerde MPS I patiënten voorafgaand aan een geplande HSCT is effectief in het verbeteren van de conditie van de patiënt voorafgaand aan de transplantatie. De zeldzaamheid van de ziekte, in combinatie met de complexiteit van de ziekte en de complexe overwegingen rondom behandeling, maakt dat behandeling van MPS I met laronidase het beste kan plaatsvinden in expert centra (thans Erasmus MC in Rotterdam en AMC in Amsterdam).

Introduction

1.1 Laronidase

Composition: Laronidase 100 U (approximately 0.58 mg) per ml.
Laronidase is a recombinant form of human α-L-iduronidase and is produced by recombinant DNA technology using mammalian Chinese Hamster Ovary cell culture.

Method of administration: intravenous infusion.

Recommended dose: 100 U per kg body weight administered once every week.

Mechanism of action: α-L-iduronidase is a lysosomal hydrolase that catalyses the hydrolysis of terminal α-L-iduronic acid residues of the glycosaminoglycans (GAG) dermatan sulfate and heparan sulfate. The rationale of laronidase therapy in MPS I is to provide exogenous enzyme for uptake into lysosomes and increase the catabolism of accumulated GAGs and prevent further accumulation.

1.2.a Registered indications for laronidase

Laronidase is indicated for long-term enzyme replacement therapy (ERT) in patients with a confirmed diagnosis of MPS I to treat the non-neurological manifestations of the disease.

1.2.b Indications for which registration is requested

As reported in this review, it is the opinion of the authors, based on the literature and their expert opinion, that laronidase should also be prescribed for short-term treatment of selected patients with a confirmed diagnosis of MPS I who are referred for HSCT *prior* to HSCT. It is highly debatable if this truly concerns “off label” use, as it is aimed at treating non-neurological manifestations of MPS I. The caveat is the interpretation of the word “long- term”, as the use of laronidase prior to HSCT is in general for the duration of several months.
We propose to either leave out the words “long-term” in de registered indication, or change this sentence into: “Laronidase is indicated for long-term enzyme replacement (ERT) in patients with a confirmed diagnosis of MPS I, or for short-term use in patients with a confirmed diagnosis of MPS I awaiting HSCT, to treat the non-neurological manifestations of the disease”.

1.3 Current reimbursement of laronidase

Laronidase has been granted orphan drug status and is only intramurally reimbursed by the policy rule on orphan drugs (CU-2000).

1.4 Signs and symptoms for which laronidase is prescribed

Laronidase has been granted marketing approval in the European Union by the European Medicines Agency (EMA) and is indicated for long-term enzyme replacement therapy (ERT) in patients with a confirmed diagnosis of MPS I to treat the non-neurological manifestations of the disease. The phase III study and phase III open label extension study have shown that treatment with laronidase improves pulmonary function and walking capacity of MPS I patients (2,4). Accumulating data demonstrate that laronidase is also capable of improving or stabilizing joint range of motion (ROM) and improving activities of daily living and pain (4). Laronidase is currently prescribed to treat the above mentioned MPS I related clinical symptoms. Finally, laronidase has been shown to improve the clinical condition of selected patients who are referred for HSCT, before the HSCT procedure (7-10).

1.5 Pathophysiology of MPS I

MPS I is an autosomal recessive disorder caused by a deficiency of α-L-iduronidase, a lysosomal hydrolase which catalyses the hydrolysis of terminal α-L-iduronic acid residues of the mucopolysaccharides (also called 'glycosaminoglycans' or GAGs) dermatan sulfate and heparan sulfate. GAGs are long, unbranched polysaccharides, consisting of repeating disaccharide units, mainly localized in the extracellular matrix. GAGs have a variety of complex biological functions.

Reduced or absent α-L-iduronidase activity results in the continued accumulation and storage of these GAGs throughout the body and leads to widespread cellular, tissue, and organ dysfunction, leading to loss of function, clinical deterioration, and progressive disability. With progressive damage to organs and tissues, some changes may become irreversible.

1.6 Prevalence of the disorder

Poorthuis et al. estimated the birth prevalence of MPS I in the Netherlands as 1.19 per 100,000 live births (1:84,000) (11). Recent data from the Dutch Diagnosis Registration Metabolic Diseases (DDRMD, www.ddrmd.nl) suggest a slightly lower birth prevalence of MPS I in the Netherlands: 1: 125,000. Currently, 24 non-transplanted MPS I patients are known to be alive in the Netherlands. Of them 19 receive laronidase. One patient is treated with laronidase after HSCT, because of partial chimerism and low residual iduronidase activity.

1.7 Severity of MPS I

MPS I is generally delineated into three separate disease phenotypes on the basis of clinical presentation:

- Hurler syndrome (severe)
- Hurler-Scheie syndrome (intermediate)
- Scheie syndrome (attenuated)

More recently, the phenotypes in MPS I have been recognized as a spectrum ranging from severe (with involvement of the central nervous system resulting in cognitive decline) to attenuated (without cognitive decline). The most severe phenotype (Hurler syndrome) is characterized by an early-onset, rapidly progressive disease with early death (usually within the first two decades of life) due to cardio-respiratory and/or central nervous system (CNS) disease. In the most attenuated form of the disease (Scheie syndrome), disease progression is more slowly and without involvement of the CNS, with death at middle age or later. In the absence of treatment, patients with the Hurler-Scheie phenotype have a life expectancy of ~ 25 years or less.

Signs and symptoms that may occur in all MPS I phenotypes include hepatosplenomegaly, coarse facial features, airway disease, restriction of pulmonary function, cardiac disease, joint stiffness, skeletal deformities, ophthalmological disease, hearing loss and excessive urinary GAG excretion.

Most MPS I patients report moderate to severe physical disabilities and limitations in activities of daily living. As patients with the most attenuated form often have severe and disabling disease, even this phenotype certainly does not represent a mild disease.

1.8 Treatment of MPS I

Laronidase is the only EMA- and FDA-approved treatment for the non-neurological symptoms in MPS I. Laronidase is proven to be safe and effective across a wide range of ages (young children to adults) and disease severity (severe to attenuated) (see further sections), significantly ameliorating several of the debilitating disease related symptoms.

As intravenous laronidase is unable to cross the blood brain barrier it is not expected to prevent cognitive decline, or improve CNS disease, in patients with the severe phenotype of MPS I (Hurler syndrome). ERT is used for selected Hurler patients for whom HSCT in not an option, as it may improve quality of life and relieve pain. However, no studies have been done on this indication for treatment with laronidase. HSCT is the treatment of choice for the group of Hurler patients, but should probably only be attempted in a selected group of severely affected patients, preferably before the age of 2.5 years and with a developmental quotient (DQ) > 70 at the time of transplantation. If HSCT is performed in time it may preserve intellectual development in this group of patients. Because the procedure carries significant risks, including increased morbidity and mortality, HSCT is justified only in the severe, Hurler, phenotype and not in the attenuated, Scheie, phenotype. Whether HSCT is justified in the intermediate phenotype remains to be established.

1.9 Proposed indication of laronidase in the treatment of MPS I

Laronidase is indicated for the long-term treatment of non-neurological disease manifestations in patients with a confirmed diagnosis of MPS I.

Recently (September 28, 2010) a group of recognized European experts, highly experienced in the treatment of patients with MPS I, met in Amsterdam to obtain consensus on the indications for ERT

and/or HSCT in patients with MPS I. This '*European Consensus Meeting on ERT and/or HSCT*' was organized and executed in collaboration with the department 'Clinical Epidemiology in Pediatrics' (KEK, AMC, Amsterdam), and supervised by Prof.dr. M. Offringa. The consensus meeting was preceded by a process designed to extract critical issues used for decision making on optimal therapy. These issues were subsequently discussed during the meeting.

Eight experts on ERT in MPS I and seven experts on HSCT in MPS I participated (see ***addendum 3*** for a list of specialists and their affiliations involved in this European consensus project).

Full (100%) consensus was reached on several critical items:

1. **The preferred treatment strategy for patients homozygous or compound heterozygous for mutations clearly associated with the severe ('Hurler') phenotype AND/OR patients diagnosed before the age of approximately 2.5 years on clinical signs and symptoms compatible with the severe 'Hurler phenotype'(i.e. phenotypical diagnosis based on clinical expertise) is HSCT.**

   Rationale:

   ERT is not effective in preventing neurocognitive decline in patients with the 'Hurler phenotype' as the recombinant enzyme will not cross the blood-brain barrier in sufficient quantity (1-5). Early treatment by HSCT may preserve cognition and may ameliorate or prevent several of the somatic manifestations of the disease (12-15). In addition, advances in chemotherapeutic conditioning and donor selection have significantly improved the outcome of this procedure (15, 16). Therefore, HSCT is the preferred treatment for patients with the severe 'Hurler phenotype' (*full consensus experts*).
2. **All (not transplanted) MPS I patients may benefit significantly from ERT as this will ameliorate several somatic symptoms of the disease.**

   Rationale:

   Clinical trials have demonstrated that ERT is safe and effective in patients with MPS I across a wide range of ages (young children to adults) and phenotypes (severe and attenuated) (1-6). Long-term ERT effectively treats several somatic signs and symptoms of MPS I, resulting in improved quality of life (3,4).
3. **As the efficacy of ERT improves if initiated at an early age, ERT should be started at diagnosis in symptomatic patients.**

   Rationale:

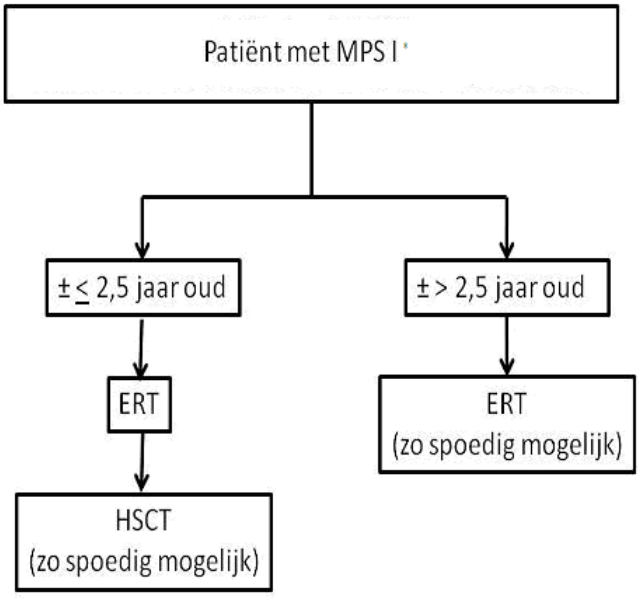
   End organ damage, associated with progressive GAG accumulation, may worsen and become irreversible in untreated MPS I patients (*full consensus experts*). Therefore, initiation of treatment early in the disease course is likely required to prevent and/or minimize irreversible damage at least in symptomatic patients (*full consensus experts*). A case history on siblings started on ERT at different ages supports this statement (17).
4. **Patients who are referred for HSCT may benefit from ERT before HSCT as this can improve the clinical condition of the patient.**

   Rationale:

   The clinical condition of a patient at the time of transplantation will influence the morbidity and mortality of the HSCT (*full consensus experts*). Since ERT has shown to result in a significant and

relatively rapid improvement of respiratory and cardiovascular function (1-5), ERT may ameliorate the pre-transplant condition of a patient. It was shown that ERT prior to HSCT is well tolerated and may significantly improve the pre-transplant condition in selected patients (7-10). In addition, there is evidence that ERT does not negatively influence engraftment (7-10). However, initiating ERT should not delay the transplant, unless the clinical condition of the patient precludes HSCT (*full consensus experts*).

These European consensus statements result in the following treatment strategy for MPS I patients: :



* Diagnosis based on deficient α-L-iduronidase activity and/or mutational analysis.

The presented treatment strategy is meant as a general guideline. The broad phenotypic spectrum precludes developing a treatment algorithm that fits all MPS I patients. Starting as well as stopping of treatment should always be considered on an individual, patient by patient, basis.

2. Methods

2.1 Alternative treatment option(s)

Since treatment with laronidase is the only long-term treatment option for patients with MPS I who do not qualify for, or have not had, a (successful) HSCT, the long-term treatment effects of laronidase are compared with the natural history of the disease, i.e.: a progressive multi-system disease.

2.2 Review of the literature

In September 2010, an electronic search was conducted using Pubmed and EMBASE to identify all relevant articles. Criteria used as key words were: mucopolysaccharidosis I, MPS I, Aldurazyme, Laronidase, alpha-L-iduronidase and enzyme replacement therapy. In addition, the CFH report 'laronidase (Aldurazyme®)' (CFH-report 03/15, July 10, 2003) was used as a reference.

2.3 Relevant clinical trials

Most relevant publications (clinical trials) (see also addendum 4 and table 1):

The following clinical trials (a-f) were considered most relevant because of the, as rated by us, higher methodological quality of the trials, and includes the only RCT available at present.

a) Phase I/II clinical trial:

Kakkis, et al. Enzyme replacement therapy in mucopolysaccharidosis I. N Engl J Med 2001;344:182-8.

b) Phase III clinical trial:

Wraith, et al. Enzyme replacement therapy for mucopolysaccharidosis I: a randomized, double-blinded, placebo-controlled, multinational study of recombinant human alfa-l-iduronidase (laronidase). J Pediatr 2004;144:581-8.

c) Phase I/II extended clinical trial:

Sifuentes, et al. A follow-op study of MPS I patients treated with laronidase enzyme replacement therapy for 6 years. Mol Genet Metab 2007;90:171-180.

d) 'Less than 5 years study':

Wraith, et al. Enzyme replacement therapy in patients who have mucopolysaccharidosis I and are younger than 5 years: results of a multinational study of recombinant human alfa-l-iduronidase (laronidase). Paediatrics 2007;120(1):e37-46.

e) Phase III extended clinical trial:

Clarke, et al. Long-term efficacy and safety of laronidase in the treatment of mucopolysaccharidosis I. Pediatrics 2009;123:229-240.

f) Dose-optimization trial:

Giugliani, et al. A dose-optimization trial of laronidase (Aldurazyme) in patients with Mucopolysaccharidosis I. Mol Genet Metab 2009;96:13-19.

Additional relevant publications (see also addendum 4 and tables 2 and 3):

g) Cox-Brinkman, et al. Restricted upper extremit

y range of motion in mucopolysaccharidosis type I: no response to one year of enzyme replacement therapy. J Inherit Metab Dis 2007;30:47-50.

h) Arora, et al. Enzyme replacement therapy in 12 patients with MPS

I–H/S with homozygous p.Leu490Pro mutation. J Inherit Metab Dis 2007;30:821.

i) Gabrielli, et al. Enzyme replacement therapy in a 5-month-old boy with attenuated presymptomatic MPS I: 5-year follow-up. Pediatrics 2010;125:e183-e187.

j) Tylki-Szymanska, et al. Anthropometric data of 14 patients with MPS I: retrospective analysis and efficacy of recombinant human alfa-L-iduronidase. Mol Genet Metab 2010;99:10-17.

k) Tylki-Szymanska, et al. Efficacy of recombinant human α-L-iduronidase (laronidase)

on restricted range of motion of upper extremities in mucopolysaccharidosis type I patients. J Inherit Metab Dis (2010) 33:151–157.

l) Grewal, et al. Safety and efficacy of enzyme replacement therapy in combination with hematopoietic stem cell transplantation in Hurler syndrome. Genet Med 2005;7:143-6.

m) Cox-Brinkman, et al. Haematopoietic cell transplantation (HCT) in combination with enzyme replacement therapy (ERT) in patients with Hurler syndrome. Bone Marrow Transplant 2006;38:17-21.

n) Tolar, et al. Combination of enzyme replacement and hematopoietic stem cell transplantation as therapy for Hurler syndrome. Bone Marrow Transplant 2008;41:531-535.

o) Wynn et al. Use of enzyme replacement therapy (Laronidase) before hemaptopoietic stem cell transplantation for Mucopolysaccharidosis I: experience in 18 patients. J Pediatr 2009;154:135-9.

Table 1. Clinical studies on enzyme replacement with laronidase in MPS I patients

First author, **Publication year**	Kakkis, 2001	Wraith, 2004	Sifuentes, 2007	Wraith, 2007	Clarke, 2009	Giugliani, 2009
Study as mentioned in this paper	Study a	Study b	Study c	Study d	Study e	Study f
Study type	Phase 1/2	Phase 3	Phase 1/2 Extension	Under 5 years	Phase 3 Extension	Dose-optimization
Patient number	10	45	5	20	40	33
Phenotype distribution	10% Hurler 80% Hurler-Scheie 10% Scheie	2% Hurler 82% Hurler-Scheie 16% Scheie	80% Hurler-Scheie 20% Scheie	80% Hurler 20% Hurler-Scheie	84% Hurler-Scheie 16% Scheie	30% Hurler 49% Hurler-Scheie 21% Scheie
Mean age at baseline (years)	12.3 Range: 5-22	15.5 Range: 6-43	12.0 Range: 8-17	2.9 Range: 0.5-5.1	15.7 Range: 6.3-43.3	8.9 Range: 1.4-20.7
Intervention (Laronidase)	100 U/kg/week	100 U/kg/week vs. placebo	100 U/kg/week	100 U/kg/week; 4 patients 200 U/kg/week after 26 weeks	100 U/kg/week	100 U/kg/week 200 U/kg/week 200 U/kg/2 wks 300 U/kg/2 wks
Follow-up	52 weeks	26 weeks	5 years	52 weeks	3.5 years	26 weeks
Primary endpoints	Liver/spleen volume Urinary GAG levels	Percent of predicted FVC Distance covered in the 6-MWT	Liver/spleen volume Urinary GAG levels	Urinary GAG levels Liver size Cardiac function	Percent of predicted FVC Distance covered in the 6-MWT	Urinary GAG levels
Secondary endpoints	Joint mobility Growth Apnoea/hypopnoea Cardiac function Functional ability Visual acuity	Liver volume Urinary GAG levels Joint mobility Apnoea/hypopnoea Functional ability	Growth Joint mobility Cardiac function Apnoea/hypopnoea Visual acuity Neurological status Appearance Quality of life	Apnoea/hypopnoea	Liver volume Urinary GAG levels Joint mobility Apnoea/hypopnoea Functional ability Visual acuity Cardiac function Growth	Liver volume Distance covered in the 6-MWT

Table 2. Clinical studies on enzyme replacement with laronidase in MPS I patients

First author, **Publication year**	Cox-Brinkman, 2007	Arora, 2007	Gabrielli, 2009	Tylki-Szymanska, 2010	Tylki-Szymanska, 2010
Study as mentioned in this paper	Study g	Study h	Study i	Study j	Study k
Study type	Single-institutional, prospective cohort trial	Single-institutional, retrospective cohort trial	Case report	Single-institutional, retrospective and prospective cohort trial	Single-institutional, prospective cohort trial
Patient number	6	12	2	14	17
Phenotype distribution	100% Scheie	100% Hurler-Scheie Homozygous p.Leu490Pro	100% Hurler-Scheie	64.3% Hurler 14.3% Hurler-Scheie 21.4% Scheie	59% Hurler 12% Hurler-Scheie 29% Scheie
Mean age at baseline (years)	6.3 Range: 3-11	Median: 8.6 Range: 0.4-23.1	Patient 1: 5 Patient 2: 5 months	4.8 Range: 1-15	8.1 Range: 1-39
Intervention (Laronidase)	100 U/kg/week	100 U/kg/week	100 U/kg/week	100 U/kg/week	100 U/kg/week
Follow-up	52 weeks	Median: 22.5 months Range: 2-71	5 years	Range: 52-260 weeks	Range: 50-208 weeks
Primary endpoints	Range of motion	Urinary GAG levels Hepatosplenomegaly Growth	Urinary GAG levels Hepatosplenomegaly Cardiac function Joint mobility Eye disease Hearing impairment Skeletal disease Growth Development	Height Weight Head circumference Chest circumference	Range of motion Functional status
Secondary endpoints	Functional status			Urinary GAG levels	

Table 3. Clinical studies on enzyme replacement with laronidase prior to HSCT in MPS I

First author, **Publication year**	Grewal, 2005	Cox-Brinkman, 2006	Tolar, 2008	Wynn, 2009
Study as mentioned in this paper	Study l	Study m	Study n	Study o
Study type	Multi-institutional, retrospective case series	Multi-institutional, retrospective cohort study	Single-institutional, prospective trial	Single-institutional, prospective cohort study
Patient number	12	22	7	18
Phenotype distribution	100% Hurler	100% Hurler	100% Hurler	100% Hurler
Age (months)	At initiation of ERT: Median: 12 Range: 8-18	Age at HSCT: Median: 18 Range: 2-39	Age at HSCT: Median: 18 Range: 8-23	Age at HSCT: Mean: 12 Range: 7-24
Intervention (Laronidase)	100 U/kg/week	100 U/kg/week	100 U/kg/week	100 U/kg/week
Duration of pre-HSCT ERT (weeks)	Median: 12 Range: 4-28	Median: 12 Range: 7-24	Range: 11-14	≥ 12
Duration of post-HSCT ERT (weeks)	Median: 7 Range: 3-20	Median: 12 Range: 0-12	8	Until engraftment
Follow-up **(months after HSCT)**	Median: 3 Range: 1-7	Median: 8.5 Range: 3-17.5	Range: 6-29	≥ 6
Primary endpoints	Pulmonary complications associated with HSCT	The 'alive and engrafted rate'	Engraftment Pulmonary complications associated with HSCT	Overall survival Engraftment rate
Secondary endpoints	Donor engraftment Urinary GAG levels	HSCT-associated morbidity	Overall morbidity	HSCT-associated morbidity

3. Therapeutic value

3.1 Beneficial effects of laronidase

3.1.1 Outcome parameters

- Improvement in respiratory function.
  A clinically relevant parameter, since progressive respiratory disease in MPS I leads to shortness of breath, fatigue, daytime somnolence, pulmonary hypertension/cor pulmonale, and increased vulnerability to pulmonary infections. The latter two compose a significant problem and common cause of death in MPS I patients. Improvement of respiratory function is generally quantified by measuring Forced Vital Capacity (FVC) as this parameter can be measured reliably in (older) patients with MPS I, and this parameter is included.
- Improvement in walking ability (e.g. 6-MWT).
  A clinically relevant parameter, since it influences quality of life and 'activities of daily living (ADL)' in MPS I patients.
- Improvement in range of motion.
  A clinically relevant parameter, since improvements in the range of motion may accompany increases in physical activities and quality of life.
- Improvement in growth patterns.
  Anthropometric features of patients with MPS I differ significantly from the healthy population. A major feature of affected patients can be marked dwarfism. This can be a clinically relevant problem for MPS I patients.
- Reduction in hepatomegaly.
  The degree of reduction in hepatomegaly indicates effective clearance of accumulated GAGs in affected patients. In addition, the sometimes significant hepatomegaly can negatively impact respiratory function.
- Improvement in cardiac disease.
  A clinically relevant parameter, since severe cardiac disease (e.g. cardiomyopathy) may lead to early death in MPS I patients.

3.1.2 Motivation for excluding outcome parameters

Urinary GAG-excretion: the degree of reduction in urinary GAG-excretion indicates a biochemical response to ERT, probably consisting of clearance of accumulated GAGs. Urinary excretion of GAGs was used as a primary outcome parameter in several of the most relevant clinical trials. However, the authors

of this review consider the level of urinary excretion of GAGs not as a clinically relevant outcome measurement. To our knowledge, there are no studies demonstrating a correlation between urinary GAG levels and improvement (or deterioration) of clinical signs and symptoms. This relates to the non-specific nature of GAG measurement as well as the fact that urinary GAGs are likely reflective of renal tubular involvement/dysfunction rather than total body disease burden in the MPSs. However, to complete the results of the most relevant clinical trials, the results of the reduction in GAG levels are reported in table 4.a-e and table 5.

More recent studies have shown that the plasma concentration of 'the heparin cofactor II – thrombin complex' may prove to be an import biomarker for monitoring therapeutic efficacy of laronidase in MPS I (Clarke LA, J Inherit Metab Dis, 2011, Jul 6, epub ahead of print). However, more studies, preferably prospective, are needed to establish its true potentials.

3.1.3 Efficacy of laronidase on relevant outcome parameters

Efficacy as deducted from most relevant publications (table 1, see above).

The phase I/II study (open label, 10 patients, table 4.a, see below) showed rapid and significant reductions in liver volume after 52 weeks of treatment. In addition, an increase in height and weight, improvement in range of motion and increase in physical activities, a decrease in the incidence of sleep apnoea and hypopnoea and an improvement in heart function was noted during the study (1).

The extended phase I/II trial, (5 patients, table 4.b, see below) revealed that liver volume further reduced to normal in nearly all patients by 1 year and continued to fall steadily to below the mean normal level over the 6-year period, while various other clinically relevant disease parameters showed further improvement (shoulder range of motion, sleep apnoea as a measure of respiratory function) or remained stable (sleep apnoea in several patients) after six years of treatment. These trends towards improvement (not significant) contrast the natural history of the disease which predicts an ongoing deterioration in all these areas. Although pre-existing heart valve disease did progress in some patients, cardiac disease showed no progression to heart failure (3).

The phase III study (RCT, 45 patients, table 5, see below) showed a statistically significant increase in respiratory function as measured by forced vital capacity. Walking ability as measured by the 6-minute walk test and apnoea-hypopnoea index as a measure of respiratory function improved compared to the placebo group after 26 weeks of treatment. After post-hoc ANCOVA analysis these improvements were significant. In addition, patients receiving laronidase showed a significant reduction in liver volume. In patients with shoulder flexion below the baseline median, a positive trend was noted in patients receiving laronidase (2).

The extended phase III trial (40 patients, table 4.c, see below) showed stabilization or further improvements in most patients with respect to respiratory function, walking ability, liver volume, joint range of motion and quality of life (4).

The phase III study required that patients were capable of performing a reproducible pulmonary function test and 6-minute walk test and therefore excluded patients younger than 5 years of age. Therefore, the

safety and efficacy of laronidase in patients less than 5 years was evaluated in a separate study (5). This 'under 5 years-study' (20 patients, table 4.d, see below) showed improvements in liver volume, left ventricular hypertrophy and apnoea-hypopnoea index. The degree of reduction in hepatomegaly indicated effective clearance of accumulated glycosaminoglycan substrates in young and severely affected patients, consistent with the treatment effect that was observed in older patients.

A dose-optimization study (33 patients, table 4.e, see below) showed no major differences in efficacy between the currently approved laronidase dose and alternative regimens (6). Reduction in liver volume was significant on all tested doses. Mean improvement in walking ability (as measured by the 6 minute walk test) was not significant in this 26-weeks study.

Efficacy as deducted from the additional relevant publications (tables 2 & 3, see above).
A 12-months study in six attenuated MPS I patients failed to show significant improvement in large joint range of motion at different time intervals (18). However, from other studies (e.g. the phase III extension study) it has become clear that it takes longer for some of the effects of laronidase to become apparent. In addition, a more recent study on the effectiveness of laronidase on the range of motion of upper extremities of patients with MPS I shows that introduction of ERT led to slower progression of symptoms, especially in the passive range of motion in all patients (19).

Another study, a cohort of 14 Hurler-Scheie patients homozygous for the p.Leu490Pro missense mutation, showed a clear improvement in liver- and spleenvolume after 24 months of treatment, however, no clear conclusions could be drawn with regard to the efficacy of ERT for growth (20). In a more recent study, no effect of laronidase on growth patterns of MPS I patients was shown, even after 104-260 weeks of treatment (21).

A case-report on the 5-year follow-up of an initially asymptomatic boy with attenuated MPS I in whom laronidase was started from the age of 5 months compares his clinical course to that of his older sister, who began treatment at 5 years of age. A comparison of the clinical features in these children at the age of approximately 5 years provides compelling evidence that early ERT might prevent the development of major clinical features of MPS I (17).

Use of ERT prior to HSCT has been shown to be safe in a limited number of trials (7-10) and has the potential to improve the clinical condition of patients before the HSCT procedure, which may improve HSCT-related morbidity and mortality (9,10).

Tables 4.a. – 4.e. and table 5 show the results of laronidase on the most relevant clinical parameters.

Table 4.a. Efficacy of laronidase in MPS I patients, after 52 weeks of treatment [1]

N/A: not available or not applicable

* In six prepubertal patients

	[laronidase] *(n = 10)*	*p*
Primary endpoints	Mean decrease in liver volume 25%	<0.001
	Mean reduction in urinary GAG levels 63%	<0.001
Secondary endpoints	Mean increase in rate of height growth 85%*	0.01
	Mean decrease in shoulder restriction (R) 28°	< 0.001
	Mean decrease in shoulder restriction (L) 26°	0.002
	Cardiac function improved in all patients	0.002
	Decrease in AHI 61%	N/A
	Functional ability improved in all patients	N/A

Table 4.b. Efficacy of laronidase in MPS I patients, after 6 years of treatment [3]

N/A: not available or not applicable

	[laronidase] *(n = 5)*	*p*
Primary endpoints	Mean reduction in liver volume > 20%	<0.0001
	Mean reduction in urinary GAG levels 77%	0.0004
Secondary endpoints	Mean increase in height 27%	N/A
	Mean increase in shoulder flexion (R) 33.2°	N/A
	Mean increase in shoulder flexion (L) 25.0 °	N/A
	Cardiac function improved in 80% of patients	0.1250
	Decrease in AHI in 80% of patients	N/A
	Functional ability improved in all patients	N/A

Table 4.c. Efficacy of laronidase in MPS I patients, after 3.5-4 years of treatment [4][1]

[1] No p-values reported. However, the proportion of patients whose clinical status improved, remained stable, or declined over the course of the trial was determined by using specific predefined thresholds (see article) (2).

	[laronidase] *(n = 40)*	*Results*
Primary endpoints	Mean decline in FVC 0.78% per year	73% improved or stable
	Mean improvement in 6-MWT 17.1 m	78% improved or stable
Secondary endpoints	Mean reduction in urinary GAG levels 72%	72% ≤ + 2 SD of normal
	Mean decrease in liver volume 38%	95% within normal values
	Mean increase in shoulder flexion 17.4 °	95% improved or stable
	Mean reduction in AHI 4.4 events per h	94% improved or stable
	Mean improvement in disability index 0.31	77% improved or stable
	Median height velocity	normalized in all pediatric patients

Table 4.d. Efficacy of laronidase in MPS I patients < 5 years, after 52 weeks of treatment [5]

N/A: not available or not applicable

* In patients with clinically significant abnormal baseline values

	[laronidase] *(n = 20)*	*Results*
Primary endpoints	Mean decrease in liver edge 69.5%	50% within normal values
	Mean reduction in urinary GAG levels 61.3%	N/A
	Mean decrease in cardiac z-score 11.3%	N/A
Secondary endpoints	Mean decrease in AHI 8.5%*	clinically significant in 33%

Table 4.e. Results of a dose-optimization study on laronidase in MPS I patients, after 26 weeks of treatment [6]

	[laronidase] *(n = 33)*	*95% CI*
Primary endpoints	Mean reduction in urinary GAG levels (100 IU/kg/wk) 58%	[42,73%]
	Mean reduction in urinary GAG levels (200 IU/kg/wk) 66%	[54,80%]
	Mean reduction in urinary GAG levels (200 IU/kg/2wks) 66%	[59,73%]
	Mean reduction in urinary GAG levels (300 IU/kg/2wks) 63%	[58,68%]
Secondary endpoints	Mean decrease in liver volume (100 IU/kg/week) 26%	[19,34%]
	Mean decrease in liver volume (200 IU/kg/week) 31%	[23,38%]
	Mean decrease in liver volume (200 IU/kg/2wks) 31%	[15,46%]
	Mean decrease in liver volume (300 IU/kg/2wks) 32%	[24,41%]
	Mean change in 6-MWT (100 IU/kg/week) + 7m	[-80,94]
	Mean change in 6-MWT (200 IU/kg/week) -12 m	[-73,49]
	Mean change in 6-MWT (200 IU/kg/2wks) + 25 m	[-44,95]
	Mean change in 6-MWT (300 IU/kg/2wks) + 52 m	[-15,119]

Table 5. Efficacy of laronidase in MPS I patients, after 26 weeks of treatment; a randomized controlled trial [2]

N/A: not available or not applicable

	[laronidase] *(n = 22)*	*[placebo]* *(n = 23)*	*Mean difference* *(p)*
primary endpoints			
- Mean improvement in FVC	4.9%	-0.7%	5.6% (median 3.0; p=0.009)
- Mean change in 6-MWT	19.7 m	-18.4 m	38.1m (median 38.5; p=0.066)
secondary endpoints			
- Mean change in urinary GAG levels	- 54.1%	+47.3%	101.4% (< 0.001)
- Mean change in liver volume	-18.9%	+1.3%	20.2% (0.001)

- Mean change in AHI	N/A	N/A	3.6 events per h (0.145)
- Mean change in shoulder flexion	+9.6°	-4.8°	14.4° (not significant)

3.2 Adverse effects of laronidase

Adverse effects consist mainly of 'infusion associated reaction' (IAR's), which are hypersensitivity reactions (IgG mediated) to the intravenous enzyme. Symptoms usually resolve after the infusion is stopped. The incidence of infusion reactions appears to decrease with time. Treatment of patients showing infusion associated reactions could be continued by reducing the rate of infusion and by the use of prophylactic drugs (antihistamines/antipyretics), administered approximately 60 minutes prior to the start of the infusion. Patient with an acute underlying illness at the time of laronidase infusion appear to be at greater risk for IAR's.

Reporting on IAR's in the most relevant studies:

- Kakkis et al, 2001: five (of 10) patients had transient urticaria during infusions. In three (of 10) patients, urticaria was accompanied by angioedema and by moderate transient hypoxemia. One (of 10) patient had fever, chills and 'fussy behavior'.
- Wraith et al, 2004: Infusion-related reactions consisted mainly of flushing, fever, headache and rash and had a similar patient incidence in the Laronidase and placebo groups (32% vs 48%). Most reactions were mild. No medical intervention or interruption of infusion was required.
- Sifuentes et al, 2007: only one adverse event (mild abdominal pain) met the reporting criteria as defined in the study protocol.
- Wraith et al, 2007: all patients experienced at least one adverse event. The majority of these were related to the underlying disease. Most commonly reported adverse events: pyrexia, diarrhoea, vomiting, cough, rhinorrhea, rhinitis, and rash (> 50%).
- Clarke et al, 2009: adverse events related to treatment were reported in 67% of patients. Adverse events that occurred in at least 10% of patients were: rash (22%), arthralgia (20%), headache (18%), flushing (16%), injection site reaction (13%), arthropathy (11%), abdominal pain (11%), back pain (11%), fever (13%), skeletal pain (11%) and nausea (11%). Serious adverse events occurred in two patients: hypotension and vomiting and respiratory difficulty and anaphylaxis.
- Giugliani et al, 2009: Drug-related adverse events were reported in 61% of patients. Patients in the

lowest dose group had the lowest rate of adverse events. Adverse events consisted mainly of pyrexia (21%), vomiting (15%), rash (15%), and urticaria (12%). One death due to respiratory failure was reported. Although the event was assessed unlikely related to treatment with laronidase, a possible causal relationship could not be ruled out.

Adverse drug events reported during the phase III-study and its extension (2,4) in a total of 45 patients age 5 years and older and treated up to 4 years are listed below using the following categories of frequency: very common (≥ 1/10); common (≥ 1/100 to < 1/10). Due to the small patient population, an adverse drug event reported in a single patient is classified as common (EMA-Summary of Product Characteristics).

MedDRA System Organ Class	**MedDRA Preferred Term**	**Frequency**
Investigations	Body temperature increased, oxygen saturation decreased	Common
Cardiac disorders	Tachycardia	Common
Nervous system disorders	Headache	Very common
	Paraesthesia, dizziness	Common
Respiratory, thoracic and mediastinal disorders	Respiratory distress, dyspnoea, cough	Common
Gastrointestinal disorders	Nausea, abdominal pain	Very common
	Vomiting, diarrhoea	Common
Skin and subcutaneous tissue disorders	Rash	Very common
	Angioneurotic edema, swelling face, urticaria, pruritus, cold sweat, alopecia, hyperhidrosis	Common
Musculoskeletal and connective tissue disorders	Arthropathy, arthralgia, back pain, pain in extremity	Very common
	Musculoskeletal pain	Common
Vascular disorders	Flushing	Very common
	Hypotension, pallor, peripheral coldness	Common
General disorders and administration site conditions	Pyrexia, infusion site reaction	Very common
	Chills, feeling hot, feeling cold, fatigue, influenza like illness	Common
Immune system disorders	Anaphylactic reaction	Common
Psychiatric disorders	Restlessness	Common

Adverse drug events to laronidase reported during during a prospective, open-label study in a total of 20 patients under 5 years of age and mainly of the severe phenotype, treated up to 12 months (5) are listed

below. Adverse drug events were all mild to moderate in severity (EMA-Summary of Product Characteristics).

MedDRA System Organ Class	**MedDRA Preferred term**	**Frequency**
Investigations	blood pressure increased	Very common
	oxygen saturation decreased	Very common
Cardiac disorders	tachycardia	Very common
General disorders and administration site conditions	pyrexia	Very common
	chills	Very common

Table 6. Adverse reactions (EMA-summary of product characteristics)

Most frequent	Headache, nausea, abdominal pain, rash, arthralgia, backpain, pain at extremity, flushing, pyrexia, infusion site reactions, blood pressure increased, oxygen saturation decreased, tachycardia and chills.
Serious	Anaphylaxis, facial oedema, respiratory insufficiency

3.3 Experience with laronidase

Dutch experience with laronidase is limited. Although laronidase has been available for 7 years, exposure has been less than 20,000 patient-years. This is due to the rarity of the disease (3). However, for this review we decided to present the complete experience with laronidase in the Netherlands (*see **addendum1***). Since the introduction of laronidase in the Netherlands 47 patients have been evaluated for treatment at one of the two 'centers of expertise' on lysosomal storage disorders: the Erasmus Medical Center (Rotterdam) and the Academic Medical Center (Amsterdam).These two centers are the only ones prescribing laronidase in the Netherlands. HSCT for MPS I in the Netherlands is performed in the UMC Utrecht.

In the Netherlands, 20 MPS I patients are currently being treated with laronidase and are carefully supervised by experienced specialists from these two 'centers of expertise'. Ten patients have been treated with laronidase during a short term prior to HSCT (ranging from 1.5-8 months). Four patients who received laronidase as chronic treatment have died. One patient initiated on chronic laronidase treatment decided to stop treatment because this patient felt that the potential benefits of laronidase did not outweigh the burden of chronic intravenous treatment. Finally, 11 patients were not started on laronidase. Five of them received a HSCT, and no indication for laronidase prior to HSCT was present. The other 6 patients were not started on laronidase because of various and individual reasons.

In all 47 patients a careful evaluation was performed in the 'centers of expertise', in order to decide whether the patient should start with laronidase treatment. Factors relevant decision making were, amongst others, severity of the disease, the possibility for a HSCT, and expected compliance to chronic intravenous therapy.

The relatively small and heterogeneous cohort precludes clear evaluation of efficacy data in the Dutch cohort. To monitor therapeutic efficacy in this group of patients, it will be crucial to continue the current high quality data collection in all patients, in order to allow future analyses of data (addendum 5). No MPS I patients have been withdrawn from treatment with laronidase because of serious adverse events in the Netherlands.

Table 7. Dutch experience with laronidase

	laronidase
beperkt: < 3 jaar op de markt of < 100.000 voorschriften (niet-chronische indicatie)/20.000 patiëntjaren (chronische medicatie)	**X**
voldoende: ≥ 3 jaar op de markt, en > 100.000 voorschriften/20.000 patiëntjaren	
ruim: > 10 jaar op de markt	

*Bron: CFH-criteria voor beoordeling therapeutische waarde; www.fk.cvz.nl.

3.4 Applicability

Clinical trials and additional studies, although all limited in number of included patients and complex to interpret due to the range of phenotypic disease severity of the included patients, have demonstrated that ERT is safe and has clinically relevant efficacy in patients with MPS I, across a wide range of ages (young children to adults) and phenotypes (severe and attenuated).
Apart from pregnancy and lactation on which there are insufficient data, and severe hypersensivity (e.g. anaphylactic reaction) to the active substance or to any of the excipients, there are no contra-indications for the use of laronidase in MPS I patients.
Laronidase should not be administered simultaneously with chloroquine or procaine due to the potential risk of interference with the intracellular uptake of laronidase.

3.5 Ease of use

Laronidase is administered once every week by intravenous infusion. Patients with a body weight of 20 kg or less should receive a total volume of 100 ml of sodium chloride 9 mg/ml (0.9%) solution for infusion. Patients with a body weight greater than 20 kg should receive a total volume of 250 ml. The initial infusion rate of 2 U/kg/h may be incrementally increased every fifteen minutes, if tolerated, to a maximum of 43 U/kg/h. The entire infusion volume should be delivered over approximately 3 to 4 hours, and ranges from 2 to > 5 hours in the Netherlands (including time for preparation; see *addendum 2*). Pre-treatment with antihistamines and/or antipyretics, should be considered in patients with persistent or severe infusion associated reactions.

Laronidase can be administered at home or even at school or at work if during a period of approximately 6 months no serious infusion associated reactions or other side effects have been observed (22). Home therapy is considered to be less stressful and more convenient than hospital-based therapy. Patients do

not necessarily have to miss school or work on the day they receive treatment. Home therapy may therefore improve both compliance with treatment with laronidase as well as quality of life of patients. Indeed, most Dutch patients currently receive laronidase in their home. Home treatment is primarily performed by home treatment teams ('thuiszorg'), but also by the partner of the patients or the patients him- or herself (see addendum 2). An emergency protocol is provided in (the unlikely) case adverse events occur at home. Patients adhere well to the prescribed dosing regimens and ease of use should be judged in relation to the perceived effectiveness and the severity of the disorder. See *addendum 2* for more information on this from the Dutch MPS I patients on laronidase.

Table 8. Laronidase

Administration	Intravenously
Frequency	Once weekly

4. Conclusions

Conclusions and claims

Mucopolysaccharidosis type I (MPS I) is an ultra-rare (± 1 : 125,000 life births) lysosomal storage disorder and is caused by a deficiency of the lysosomal enzyme α-L-iduronidase. The clinical spectrum of the disease is very broad, ranging from a severe to attenuated phenotype. Regardless of the phenotype, however, MPS I is always a severe, debilitating and potentially life-threatening disease.
Recombinant α-L-iduronidase (laronidase, Aldurazyme®) is the only EMA- and FDA-approved treatment option for MPS I patients, and is indicated for the (long term) treatment of the non-neurological manifestations of the disease in all MPS I patients.
The CFH concluded in 2003 that, based on the limited available scientific evidence, treatment with laronidase showed reduction in urinary GAG-excretion, liver volume, pulmonary function and walking distance of MPS I patients. In addition, the CFH concluded that the available evidence was too limited to draw firm conclusions on the therapeutic value of laronidase and that further research on the safety and efficacy of laronidase was needed (CFH-report 03/15, July 10, 2003). The authors of this review have the opinion that laronidase treatment has significant and relevant therapeutic value for selected groups of MPS I patients, based on the previously and more recently available literature (A2, B & C level of evidence), as well as on their own experiences with over 11 years of laronidase treatment in MPS I (type D level of evidence; *expert opinion*).

To date, 108 patients with MPS I have been studied within the scope of prospective trials on efficacy of laronidase: 10 patients in the phase I/II trial, 45 patients in the (randomized, placebo controlled) phase III trial, 20 patients in an open labelled study on safety and efficacy in patients < 5 years and finally 33 patients in an open labelled dose-optimization trial (table 1). Five of the 10 patients in the phase I/II and 40 of the 45 patients in the phase III study were subsequently studied in long term extension studies.
In addition, 51 MPS I patients were studied in 5 open label, single centre, prospective or retrospective case cohort studies on therapeutic efficacy (table 2).
Finally, 59 patients were included in analyses on the safety and efficacy of laronidase prior to HSCT in patients with the severe Hurler phenotype of MPS I (table 3).
All studies in MPS I are hampered by a very small number of included patients, due to its ultra low prevalence, the extremely broad phenotypic spectrum of the disease with huge differences in severity and rate of progression between the different phenotypes, and the lack of biomarkers (correlating with disease severity and efficacy of therapy on clinically relevant parameters).
Despite these severe restrictions, the following conclusions can be drawn:
Efficacy of treatment with laronidase on the 6 clinically relevant outcome parameters (improvements in respiratory function, walking ability, joint range of motion, growth patterns, cardiac disease and reduction in liver volume; see 3.1.1) is demonstrated by the most relevant clinical trials (table 1 and tables 4.a – 4e and table 5) and by the additional clinical studies (table 2).
Statistically significant improvement in liver volume and respiratory functions (lung function (FVC) and Apnea-Hypopnea index (AHI)) were observed in the only RCT performed with laronidase (2). Stabilization and improvement of joint range of motion, walking ability (6 minute walk test), growth and cardiac function was observed in the open labelled studies in many patients (1,3-5). As the natural course in MPS I is characterized by a continuous progressive deterioration of clinical signs and symptoms, stabilization of disease parameters on laronidase is considered to demonstrate efficacy. In the phase III extension study (40 patients) improvement or stabilization of pulmonary function (AHI and FVC), 6 minute walk test, joint range of motion and disability index was documented (4). Stabilization and slow improvement of relevant parameters was also observed in other small open-label single-centre studies (18-21).
Several studies have demonstrated that laronidase treatment in patients with the severe Hurler phenotype waiting for a HSCT procedure may improve the pre-transplant condition (7-10).

Laronidase treatment has proven to be safe. Side effects are restricted to infusion associated reactions which respond to pre-treatment with antihistamines/antipyretics and generally subside during prolonged treatment (1-6). In addition, laronidase before HSCT does not negatively influence engraftment or outcome of HSCT (9,10).

Laronidase has been studied in all age groups and in all phenotypes. There is (inter-) national consensus on the place of laronidase in the treatment of MPS I: laronidase is indicated for all patients with MPS I who did not have had a successful HSCT or do not qualify for HSCT.

Experience with laronidase in the Netherlands is limited due to the extreme rarity of the disorder. Data

collected on all Dutch patients are presented in this review (***addendum1***), and demonstrate that the number of patients on laronidase has remained stable and is lower than the previously estimated number of 25 (CFH-report 03/15, July 10, 2003). The cost of laronidase treatment in the Netherlands is therefore also significantly lower than predicted.

Laronidase is administered by weekly (approximately 3 – 4 hr) infusions. This 'ease of use' needs to be balanced against the severity of the disease and the relentless deterioration without treatment. Compliance is very high and to the experience of the Dutch patients the burden of chronic invasive treatment is outweighted by the perceived efficacy (*see* ***addendum2***).

A MPS I Registry (www.MPSIregistry.com) was established by BioMarin Pharmaceutical (Novato, CA) and Genzyme (Cambridge, MA) as a post-marketing, observational database designed to capture clinical data of MPS I patients for characterization of the natural course of the disease and future evaluation of the long-term safety and efficacy of ERT. The captured data focus on patient demographic and disease profiles, clinical assessment data (clinical signs and symptoms of MPS I), and patient treatment status. As of May 6 2011, data from 987 patients with MPS I have been collected from physicians in over 33 countries. Of them, 522 (45%) received laronidase and no HSCT (laronidase as chronic treatment); 142 (14%) received both laronidase and HSCT, 203 (20%) received only HSCT and finally 120 (12%) received neither laronidase nor HSCT. The voluntary and observational nature of this registry has, until now, precluded reliable analysis of the data for assessment of therapeutic efficacy of laronidase.
A recent study (Verhulst K., submitted for publication) indicate an overall low source-to-database error rate in the MPS I Registry in two different substudies (2.7% (47 discrepancies out of 1715 items ; 95% confidence interval [CI] [2.2%, 3.5%]) in study 1 and 3.7% (64 discrepancies out of 1732 items; 95% CI [2.9%, 4.7%]) in study 2). In addition, no systematic errors were found. However, data on relevant outcome parameters for assessment of the therapeutic value of laronidase are not documented in the registry in a protocolized way or even not at all, again as a result of the voluntary observational nature of the data capturing. As a result, the registry, as it is, cannot be used to extract reliable data on therapeutic value of laronidase. Only future studies, using truly prospective, protocolized and focused, data procurement and entry will allow for such studies. It is debatable if this can and should be done by means of the MPS I Registry.

A methodological robust assessment of therapeutic efficacy of laronidase by studying the data collected by the two Dutch treatment centers for patients with MPS I (AMC and ErasmusMc) is not feasible due to the small number of patients in combination with the phenotypic heterogeneity of these patients. In addition, reliable longitudinal data from patients with MPS I who were not treated by laronidase are lacking, precluding a controlled study. Probably, only an international, multi-center, long-term, controlled study may lead to new data on therapeutic value of laronidase in MPS I. In addition, the use of the newly discovered potential biomarker in MPS I (the heparin cofactor II-thrombin complex) may help in future studies on therapeutic efficacy of laronidase, but further studies are needed to demonstrate its value.

In conclusion, despite the small number of patients studied and the complexity of the disorder with a broad range of phenotypic severity characterized by different rates of disease progression, trials and additional studies have shown clear benefit of treatment with laronidase on clinically relevant outcome parameters. Laronidase is indicated for all MPS I patients who do not qualify for HSCT or did not receive HSCT. Given the extreme complexity of the disease and invasiveness of the treatment, the use of laronidase should be limited to expert centers on lysosomal storage disorders, including MPS I. These expert centers should have a multi-disciplinary approach to the care for and treatment of these patients. Currently, there are two centers for lysosomal storage disorders in the Netherlands (Erasmus Medical Center, Rotterdam and the Academic Medical Center, Amsterdam) that fully qualify as expert centers for treatment of MPS I patients. These centers will continuously collect data on natural course and treatment of the MPS I patients in the Netherlands.

There are several important issues that need further exploration to determine the role of laronidase in the treatment of MPS I more precisely. These issues are specified in ***addendum 5*** (issues to explore; 'witte vlekken analyse'). The two Dutch 'centers of expertise' will take part in several of these studies.

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Addenda

1. Addendum 1: Overview of number of patients on laronidase and costs of laronidase treatment.
2. Addendum 2: MPS I Questionnaire Dutch patients with MPS I (survey by the Dutch Society for patients with inborn errors of metabolism).
3. Addendum 3: participants of the European Consensus Meeting on ERT and/or HSCT in MPS I, Amsterdam, September 28, 2010.
4. Addendum 4: relevant articles regarding treatment of MPS I with laronidase.
5. Addendum 5: issues to explore ('witte vlekken analyse').
6. Addendum 6: relevant biographies of participants in this review (on request by ZonMw).

Pharmacotherapeutical Review

Laronidase (Aldurazyme®)

Indication:

Mucopolysaccharidose type I (MPS I)

Programma

Dure Geneesmiddelen

Date: Revised version, August 26, 2011

Contact person for the review: Prof. dr. F.A. Wijburg, metabolic pediatrician
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Contents

Abbreviations 3

Summary 4

1. Introduction 7

1.1 Laronidase 7

1.2.A Registered indications for laronidase 7

1.2.B Indications for which registration is requested 7

1.3 Current reimbursement of laronidase 7

1.4 Signs and symptoms for which laronidase is prescribed 7

1.5 Pathophysiology of MPS I 8

1.6 Prevalence of the disorder 8

1.7 Severity of MPS I 8

1.8 Treatment of MPS I 9

1.9 Proposed indication of laronidase in the treatment of MPS I 9

2. Methods 12

2.1 Alternative treatment option(s) 12

2.2 Review of the literature 12

2.3 Relevant clinical trials 12

3. Therapeutic value 17

3.1 Beneficial effects of Laronidase 17

3.1.1 Outcome parameters 17

3.1.2 Motivation for excluding outcome parameters 17

3.1.3 Efficacy of Laronidase on relevant outcome parameters 18

3.2 Adverse effects of Laronidase 22

3.3 Experience with Laronidase 24

3.4 Applicability 25

3.5 Ease of use 25

4. Conclusions 26

References 28

Addenda 29

Abbreviations

6-MWT	6-Minute Walk Test
AHI	Apnoea-Hypopnoea Index
CFH	Commissie Farmaceutische Hulp
CNS	Central Nervous System
DQ	Developmental Quotient
EMA	European Medicines Agency
ERT	Enzyme Replacement Therapy
FDA	Food and Drug Administration
FVC	Forced Vital Capacity
GAG	Glycosaminoglycan
HSCT	Hematopoietic Stem Cell Transplantation
IAR	Infusion-associated reaction
IQ	Intellectual Quotient
MPS I	Mucopolysaccharidosis type I
RCT	Randomized Controlled Trial
ROM	Range of Motion

Samenvatting

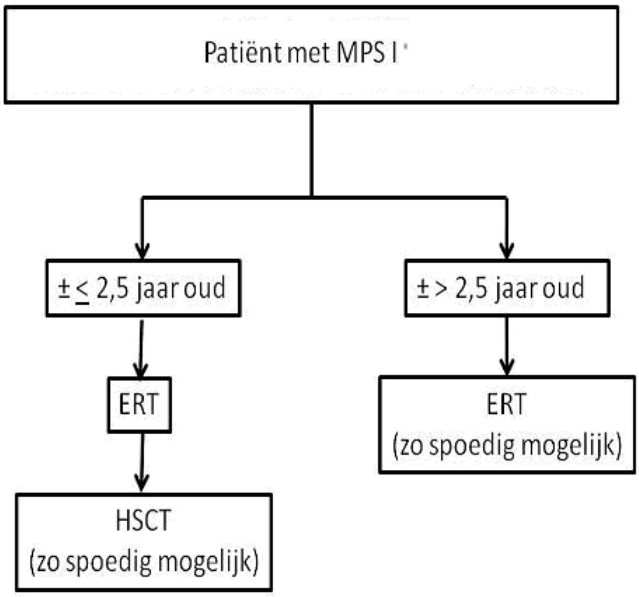
Claim van de fabrikant

Laronidase (Genzyme Corp.) is geïndiceerd voor de lange termijn behandeling van de niet-neurologische verschijnselen van patiënten met een bevestigde diagnose van de ziekte Mucopolysaccharidose type I (MPS I).

Inleiding

Laronidase is een recombinante vorm van humaan α-L-iduronidase. Laronidase wordt intraveneus toegediend (enzymvervangingstherapie, ERT) in een dosering van 100 IU/kg/week en is geïndiceerd voor de lange termijn behandeling van de niet-neurologische verschijnselen van patiënten met de ziekte MPS I.

MPS I wordt veroorzaakt door deficiëntie van het enzym α-L-iduronidase, een lysosomaal hydrolase dat nodig is om de glycosaminoglycanen (GAGs) heparan- en dermatansulfaat in het lichaam af te breken. Door stapeling van GAGs ontstaat uitgebreide en progressieve cel- en orgaanschade. MPS I kent een breed fenotypisch spectrum, variërend van relatief mild (ziekte van Scheie) tot zeer ernstig (ziekte van Hurler). Behandeling met laronidase heeft tot doel de capaciteit voor het afbreken van GAGs te vergroten en aldus verdere stapeling van GAGs te voorkomen. Omdat laronidase de bloed-hersenbarrière niet kan passeren, heeft laronidase geen effect op neurologische schade veroorzaakt door deze ziekte.



Bovenstaande figuur geeft de plaats van behandeling met laronidase (ERT) weer in het behandelschema van patiënten met MPS I. Dit behandelschema is gebaseerd op internationale consensus (zie pagina 10-12). Deze beslisboom is indicatief; per patiënt dient door de expertisecentra een individuele afweging gemaakt te worden.

* Diagnose gesteld op basis van deficiënte activiteit van α-L-iduronidase en/of mutatie-analyse.

Methoden

Behalve HSCT voor patiënten met MPS I die op grond van klinische verschijnselen al op zeer jonge leeftijd zijn gediagnosticeerd (de ziekte van Hurler), is er op dit moment geen andere oorzakelijke behandeling voor de ziekte MPS I beschikbaar.

Laronidase is geregistreerd voor de langdurige behandeling van de niet-neurologische verschijnselen van patiënten met MPS I met als doel de symptomen van de ziekte te verminderen of te stabiliseren. Het effect van laronidase kan alleen vergeleken worden met het natuurlijk beloop van de ziekte (altijd een progressieve multi-orgaan ziekte) of met placebo in randomized controlled trials (RCTs). In 2003 concludeerde de Commissie Farmaceutische Hulp (CFH) dat er op dat moment nog onvoldoende gegevens beschikbaar waren om tot een goed oordeel te komen over de therapeutische waarde van laronidase bij de behandeling van MPS I (CFH-rapport 03/15, 10 juli 2003). Voor beoordeling van therapeutische waarde baseerde de CFH zich op de fase I/II studie (1), op een deel van de resultaten van de fase I/II extensie studie, de fase III studie (2) en de eerste gegevens van de fase III extensie studie. Sinds 2003 zijn er meer data beschikbaar gekomen. De fase I/II extensie studie is gepubliceerd en geeft nu ook data over cardiale functie na langduriger behandeling (3). Daarnaast zij de langer termijn data van de fase III extensie studie beschikbaar gekomen en gepubliceerd (4). Hierin wordt de therapeutische waarde na 3.5 tot 4 jaar behandeling worden gepresenteerd (4). Tot slot zijn nog een aantal andere studies uitgevoerd om de therapeutische waarde van laronidase te bepalen, en zijn de gegevens van deze studies gepubliceerd (5,6).

De door ons op grond van methodologische overwegingen als meest relevant aangemerkte studies voor de bepaling van de therapeutische waarde van laronidase zijn de:

fase I/II–studie (10 patiënten) (1), fase III-studie (45 patiënten) (2), fase I/II- en III-extensiestudies (45 patiënten) (3,4), de studie naar het effect van laronidase bij patiënten jonger dan 5 jaar (20 patiënten) (5) en de dosering optimalisatie studie (de fase IV-studie; 33 patiënten) (6).

Daarnaast werd het therapeutisch effect van laronidase bij totaal 51 MPS I patiënten onderzocht in vijf open-label, single centre, prospectieve of retrospectieve case cohort studies en werd het effect en de veiligheid van behandeling met laronidase voorafgaand aan HSCT bestudeerd bij 59 MPS I patiënten met het ernstige (Hurler) fenotype.

Therapeutische waarde

Gunstige effecten:

De fase I/II-studie toonde aan dat intraveneuze toediening van laronidase veilig is en dat er na 52 weken behandeling sprake is van een significante afname in levervolume en tevens dat verbetering wordt waargenomen van groei, beweeglijkheid van gewrichten, hartfunctie en een afname van het optreden van slaapapneu's (1). Tijdens de 6-jaar durende follow-up studie worden deze bevindingen verder

bevestigd (3).

De fase III-studie toonde een statistisch significante toename in longfunctie en loopafstand afgelegd tijdens de 6-minuten looptest. Daarnaast wordt een significante afname beschreven van het levervolume, een afname in het optreden van slaapapneu's en een verbetering in beweeglijkheid van de gewrichten (2). De fase III-extensiestudie liet verdere verbeteringen in longfunctie, loopafstand, levervolume en beweeglijkheid van de gewrichten zien na een totale behandelduur van 4 jaar (4). Het effect van laronidase op patiënten jonger dan 5 jaar werd in een aparte studie geëvalueerd. Verbeteringen werden gerapporteerd in levergrootte, hartspierdikte en optreden van slaapapneu's na 52 weken van behandeling (5). Evaluatie van het effect van verschillende doseringen liet geen voordeel zien van andere doseringen dan die thans is geregistreerd en wordt toegepast (6).

Tot slot zijn er aanwijzingen dat er voor individuele patiënten een gunstig effect van laronidase optreedt, wanneer dit (kortdurend) toegediend wordt in de periode voorafgaand aan de HSCT (7-10).

De auteurs van dit review zijn van mening dat de therapeutische waarde van laronidase door bovengenoemd onderzoek voldoende is vastgesteld om het voorschrijven van dit middel in geselecteerde populaties van MPS I patiënten te rechtvaardigen. De 'level of evidence' van de relevante literatuur is A2 – C. Een juiste beoordeling van de kwaliteit en kwantiteit van het onderzoek is overigens alleen mogelijk indien hierbij zowel de extreme zeldzaamheid van de ziekte als de enorme fenotypische variatie van de ziekte worden meegenomen. Daarnaast hebben de twee projectleiders van het hier voorliggende review, (Prof.dr. Ans van der Ploeg, Rotterdam, en Prof.dr. Frits Wijburg, Amsterdam) beiden meer dan 11 jaar ervaring met het voorschrijven van laronidase bij patiënten met MPS I. Op grond van hun ervaring zijn zij van mening dat laronidase bij een geselecteerde groep patenten met MPS I voldoende therapeutische waarde heeft om te worden voorgeschreven (*expert opinion*, stand van de praktijk).

Ongunstige effecten:

Bijwerkingen bestaan met name uit koorts, braken, huiduitslag en urticaria. Over het algemeen zijn symptomen mild en van voorbijgaande aard. Premedicatie met antihistaminica en/of antipyretica lijkt bijwerkingen te kunnen voorkomen. Bijwerkingen doen zich voornamelijk voor aan het begin van de behandeling en nemen af naarmate patiënten langer behandeld worden. Ernstiger reacties, zoals anafylaxie en respiratoire insufficiëntie kunnen optreden, maar zijn zeer zeldzaam (1-6).

Nederlandse ervaring:

Omdat MPS I uiterst zeldzaam is, is de ervaring met laronidase in Nederland beperkt (addendum 1). Sinds het beschikbaar komen van laronidase als behandeling voor MPS I, zijn 47 patiënten met MPS I beoordeeld voor mogelijke behandeling met laronidase in de enige twee expertise centra van waaruit Laronidase in Nederland wordt voorgeschreven (ErasmusMC, Rotterdam, en AMC, Amsterdam). Op dit moment (december 2010) worden in Nederland 20 patiënten langdurig behandeld met laronidase. Dit is 5 patiënten minder dan het aantal patiënten dat in 2003 door de CFH geschat werd voor langdurige laronidase behandeling in aanmerking te komen (CFH-rapport 03/15, 10 juli 2003). De kosten voor laronidase gebruik in Nederland (gegevens december 2010) zijn dan ook nu per jaar ruim € 1, 5 miljoen lager dan aanvankelijk begroot door de CFH (CFH-rapport 03/15, 10 juli 2003). Daarnaast is bij 10 patiënten kortdurend (variërend van 1,5–8 maanden) laronidase gegeven voorafgaand aan een HSCT. Er zijn 4 patiënten die chronisch laronidase gebruikten overleden. Bij 1 patiënt die chronisch laronidase

gebruikte is de behandeling (op verzoek van de patiënt) gestaakt. Bij 11 MPS I patiënten is afgezien is van behandeling met laronidase. Van hen ondergingen 5 een HSCT, en zijn er 6 nooit met behandeling gestart.

Door de expertise centra wordt telkens voor iedere individuele patiënt een zorgvuldige afweging gemaakt of behandeling met laronidase geïndiceerd is. Hierbij wordt de ernst van de ziekte, de eventuele mogelijkheid voor HSCT voor patiënten met het ernstige (Hurler) phenotype, de te verwachten compliantie ten aanzien van enzymtherapie en de therapeutische waarde van laronidase zoals vastgesteld in wetenschappelijk onderzoek en ervaren door de experts (*expert opinion*), in de besluitvorming betrokken.

Toepasbaarheid:

De effectiviteit van laronidase is aangetoond bij patiënten met zeer uiteenlopende ernst van de ziekte (variërend van zeer ernstig tot mild) en zeer uiteenlopende leeftijden (variërend van zeer jong tot volwassen leeftijd) (1-6). Laronidase is dan ook toepasbaar voor alle MPS I patiënten, tenzij ernstige bijwerkingen optreden (zeldzaam). Laronidase is tevens geïndiceerd voor een deel van de MPS I patiënten die een HSCT zullen ondergaan, in de periode voorafgaand aan de HSCT, om de klinische conditie voorafgaand aan de procedure te verbeteren (7-10).

Gebruiksgemak:

Laronidase wordt eenmaal per week intraveneus toegediend. Toedieningduur is ongeveer 3-4 uur en varieert van 2 tot > 5 uur, inclusief voorbereidingstijd (addendum 2). Enzymbehandeling wordt opgestart in het ziekenhuis, waarna er gestreefd wordt naar verplaatsing van de behandeling naar de thuissituatie, onder verantwoordelijkheid van de voorschrijvende specialist in het expertisecentrum. Op die manier worden onnodig hoge kosten t.g.v. infusies in het ziekenhuis voorkomen en wordt de kwaliteit van leven van de patiënt bevorderd.

Conclusie

Laronidase is geregistreerd voor de langdurige behandeling van de niet-neurologische symptomen van MPS I patiënten en is effectief en veilig gebleken in de behandeling van meerdere symptomen van patiënten met uiteenlopende ernst van de ziekte en op verschillende leeftijden. Daarmee heeft laronidase bewezen van therapeutische waarde te zijn voor een geselecteerde groep patiënten met MPS I. Relatief kortdurende behandeling van geselecteerde MPS I patiënten voorafgaand aan een geplande HSCT is effectief in het verbeteren van de conditie van de patiënt voorafgaand aan de transplantatie. De zeldzaamheid van de ziekte, in combinatie met de complexiteit van de ziekte en de complexe overwegingen rondom behandeling, maakt dat behandeling van MPS I met laronidase het beste kan plaatsvinden in expert centra (thans Erasmus MC in Rotterdam en AMC in Amsterdam).

Introduction

1.1 Laronidase

Composition: Laronidase 100 U (approximately 0.58 mg) per ml.
Laronidase is a recombinant form of human α-L-iduronidase and is produced by recombinant DNA technology using mammalian Chinese Hamster Ovary cell culture.

Method of administration: intravenous infusion.

Recommended dose: 100 U per kg body weight administered once every week.

Mechanism of action: α-L-iduronidase is a lysosomal hydrolase that catalyses the hydrolysis of terminal α-L-iduronic acid residues of the glycosaminoglycans (GAG) dermatan sulfate and heparan sulfate. The rationale of laronidase therapy in MPS I is to provide exogenous enzyme for uptake into lysosomes and increase the catabolism of accumulated GAGs and prevent further accumulation.

1.2.a Registered indications for laronidase

Laronidase is indicated for long-term enzyme replacement therapy (ERT) in patients with a confirmed diagnosis of MPS I to treat the non-neurological manifestations of the disease.

1.2.b Indications for which registration is requested

As reported in this review, it is the opinion of the authors, based on the literature and their expert opinion, that laronidase should also be prescribed for short-term treatment of selected patients with a confirmed diagnosis of MPS I who are referred for HSCT *prior* to HSCT. It is highly debatable if this truly concerns “off label” use, as it is aimed at treating non-neurological manifestations of MPS I. The caveat is the interpretation of the word “long- term”, as the use of laronidase prior to HSCT is in general for the duration of several months.
We propose to either leave out the words “long-term” in de registered indication, or change this sentence into: “Laronidase is indicated for long-term enzyme replacement (ERT) in patients with a confirmed diagnosis of MPS I, or for short-term use in patients with a confirmed diagnosis of MPS I awaiting HSCT, to treat the non-neurological manifestations of the disease”.

1.3 Current reimbursement of laronidase

Laronidase has been granted orphan drug status and is only intramurally reimbursed by the policy rule on orphan drugs (CU-2000).

1.4 Signs and symptoms for which laronidase is prescribed

Laronidase has been granted marketing approval in the European Union by the European Medicines Agency (EMA) and is indicated for long-term enzyme replacement therapy (ERT) in patients with a confirmed diagnosis of MPS I to treat the non-neurological manifestations of the disease. The phase III study and phase III open label extension study have shown that treatment with laronidase improves pulmonary function and walking capacity of MPS I patients (2,4). Accumulating data demonstrate that laronidase is also capable of improving or stabilizing joint range of motion (ROM) and improving activities of daily living and pain (4). Laronidase is currently prescribed to treat the above mentioned MPS I related clinical symptoms. Finally, laronidase has been shown to improve the clinical condition of selected patients who are referred for HSCT, before the HSCT procedure (7-10).

1.5 Pathophysiology of MPS I

MPS I is an autosomal recessive disorder caused by a deficiency of α-L-iduronidase, a lysosomal hydrolase which catalyses the hydrolysis of terminal α-L-iduronic acid residues of the mucopolysaccharides (also called 'glycosaminoglycans' or GAGs) dermatan sulfate and heparan sulfate. GAGs are long, unbranched polysaccharides, consisting of repeating disaccharide units, mainly localized in the extracellular matrix. GAGs have a variety of complex biological functions.

Reduced or absent α-L-iduronidase activity results in the continued accumulation and storage of these GAGs throughout the body and leads to widespread cellular, tissue, and organ dysfunction, leading to loss of function, clinical deterioration, and progressive disability. With progressive damage to organs and tissues, some changes may become irreversible.

1.6 Prevalence of the disorder

Poorthuis et al. estimated the birth prevalence of MPS I in the Netherlands as 1.19 per 100,000 live births (1:84,000) (11). Recent data from the Dutch Diagnosis Registration Metabolic Diseases (DDRMD, www.ddrmd.nl) suggest a slightly lower birth prevalence of MPS I in the Netherlands: 1: 125,000. Currently, 24 non-transplanted MPS I patients are known to be alive in the Netherlands. Of them 19 receive laronidase. One patient is treated with laronidase after HSCT, because of partial chimerism and low residual iduronidase activity.

1.7 Severity of MPS I

MPS I is generally delineated into three separate disease phenotypes on the basis of clinical presentation:

- Hurler syndrome (severe)
- Hurler-Scheie syndrome (intermediate)
- Scheie syndrome (attenuated)

More recently, the phenotypes in MPS I have been recognized as a spectrum ranging from severe (with involvement of the central nervous system resulting in cognitive decline) to attenuated (without cognitive decline). The most severe phenotype (Hurler syndrome) is characterized by an early-onset, rapidly progressive disease with early death (usually within the first two decades of life) due to cardio-respiratory and/or central nervous system (CNS) disease. In the most attenuated form of the disease (Scheie syndrome), disease progression is more slowly and without involvement of the CNS, with death at middle age or later. In the absence of treatment, patients with the Hurler-Scheie phenotype have a life expectancy of ~ 25 years or less.

Signs and symptoms that may occur in all MPS I phenotypes include hepatosplenomegaly, coarse facial features, airway disease, restriction of pulmonary function, cardiac disease, joint stiffness, skeletal deformities, ophthalmological disease, hearing loss and excessive urinary GAG excretion.

Most MPS I patients report moderate to severe physical disabilities and limitations in activities of daily living. As patients with the most attenuated form often have severe and disabling disease, even this phenotype certainly does not represent a mild disease.

1.8 Treatment of MPS I

Laronidase is the only EMA- and FDA-approved treatment for the non-neurological symptoms in MPS I. Laronidase is proven to be safe and effective across a wide range of ages (young children to adults) and disease severity (severe to attenuated) (see further sections), significantly ameliorating several of the debilitating disease related symptoms.

As intravenous laronidase is unable to cross the blood brain barrier it is not expected to prevent cognitive decline, or improve CNS disease, in patients with the severe phenotype of MPS I (Hurler syndrome). ERT is used for selected Hurler patients for whom HSCT in not an option, as it may improve quality of life and relieve pain. However, no studies have been done on this indication for treatment with laronidase. HSCT is the treatment of choice for the group of Hurler patients, but should probably only be attempted in a selected group of severely affected patients, preferably before the age of 2.5 years and with a developmental quotient (DQ) > 70 at the time of transplantation. If HSCT is performed in time it may preserve intellectual development in this group of patients. Because the procedure carries significant risks, including increased morbidity and mortality, HSCT is justified only in the severe, Hurler, phenotype and not in the attenuated, Scheie, phenotype. Whether HSCT is justified in the intermediate phenotype remains to be established.

1.9 Proposed indication of laronidase in the treatment of MPS I

Laronidase is indicated for the long-term treatment of non-neurological disease manifestations in patients with a confirmed diagnosis of MPS I.

Recently (September 28, 2010) a group of recognized European experts, highly experienced in the treatment of patients with MPS I, met in Amsterdam to obtain consensus on the indications for ERT

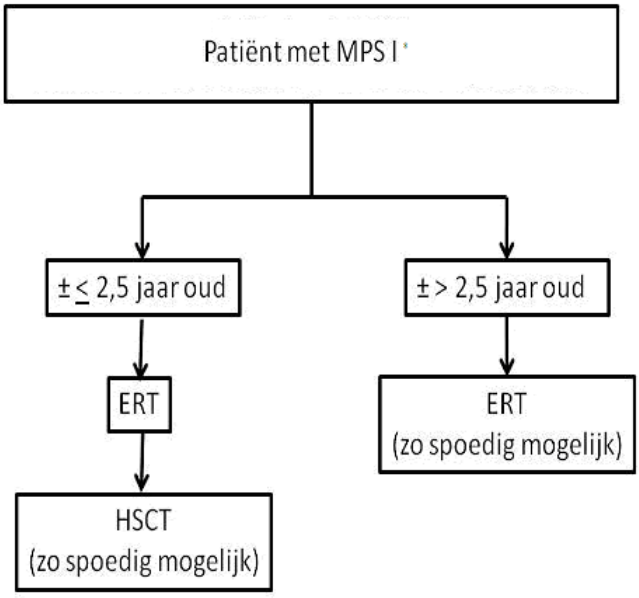
and/or HSCT in patients with MPS I. This '*European Consensus Meeting on ERT and/or HSCT*' was organized and executed in collaboration with the department 'Clinical Epidemiology in Pediatrics' (KEK, AMC, Amsterdam), and supervised by Prof.dr. M. Offringa. The consensus meeting was preceded by a process designed to extract critical issues used for decision making on optimal therapy. These issues were subsequently discussed during the meeting.
Eight experts on ERT in MPS I and seven experts on HSCT in MPS I participated (see ***addendum 3*** for a list of specialists and their affiliations involved in this European consensus project).

Full (100%) consensus was reached on several critical items:

1. **The preferred treatment strategy for patients homozygous or compound heterozygous for mutations clearly associated with the severe ('Hurler') phenotype AND/OR patients diagnosed before the age of approximately 2.5 years on clinical signs and symptoms compatible with the severe 'Hurler phenotype'(i.e. phenotypical diagnosis based on clinical expertise) is HSCT.**
   Rationale:
   ERT is not effective in preventing neurocognitive decline in patients with the 'Hurler phenotype' as the recombinant enzyme will not cross the blood-brain barrier in sufficient quantity (1-5). Early treatment by HSCT may preserve cognition and may ameliorate or prevent several of the somatic manifestations of the disease (12-15). In addition, advances in chemotherapeutic conditioning and donor selection have significantly improved the outcome of this procedure (15, 16). Therefore, HSCT is the preferred treatment for patients with the severe 'Hurler phenotype' (*full consensus experts*).
2. **All (not transplanted) MPS I patients may benefit significantly from ERT as this will ameliorate several somatic symptoms of the disease.**
   Rationale:
   Clinical trials have demonstrated that ERT is safe and effective in patients with MPS I across a wide range of ages (young children to adults) and phenotypes (severe and attenuated) (1-6). Long-term ERT effectively treats several somatic signs and symptoms of MPS I, resulting in improved quality of life (3,4).
3. **As the efficacy of ERT improves if initiated at an early age, ERT should be started at diagnosis in symptomatic patients.**
   Rationale:
   End organ damage, associated with progressive GAG accumulation, may worsen and become irreversible in untreated MPS I patients (*full consensus experts*). Therefore, initiation of treatment early in the disease course is likely required to prevent and/or minimize irreversible damage at least in symptomatic patients (*full consensus experts*). A case history on siblings started on ERT at different ages supports this statement (17).
4. **Patients who are referred for HSCT may benefit from ERT before HSCT as this can improve the clinical condition of the patient.**
   Rationale:
   The clinical condition of a patient at the time of transplantation will influence the morbidity and mortality of the HSCT (*full consensus experts*). Since ERT has shown to result in a significant and

relatively rapid improvement of respiratory and cardiovascular function (1-5), ERT may ameliorate the pre-transplant condition of a patient. It was shown that ERT prior to HSCT is well tolerated and may significantly improve the pre-transplant condition in selected patients (7-10). In addition, there is evidence that ERT does not negatively influence engraftment (7-10). However, initiating ERT should not delay the transplant, unless the clinical condition of the patient precludes HSCT (*full consensus experts*).

These European consensus statements result in the following treatment strategy for MPS I patients: :



* Diagnosis based on deficient α-L-iduronidase activity and/or mutational analysis.

The presented treatment strategy is meant as a general guideline. The broad phenotypic spectrum precludes developing a treatment algorithm that fits all MPS I patients. Starting as well as stopping of treatment should always be considered on an individual, patient by patient, basis.

2. Methods

2.1 Alternative treatment option(s)

Since treatment with laronidase is the only long-term treatment option for patients with MPS I who do not qualify for, or have not had, a (successful) HSCT, the long-term treatment effects of laronidase are compared with the natural history of the disease, i.e.: a progressive multi-system disease.

2.2 Review of the literature

In September 2010, an electronic search was conducted using Pubmed and EMBASE to identify all relevant articles. Criteria used as key words were: mucopolysaccharidosis I, MPS I, Aldurazyme, Laronidase, alpha-L-iduronidase and enzyme replacement therapy. In addition, the CFH report 'laronidase (Aldurazyme®)' (CFH-report 03/15, July 10, 2003) was used as a reference.

2.3 Relevant clinical trials

Most relevant publications (clinical trials) (see also addendum 4 and table 1):

The following clinical trials (a-f) were considered most relevant because of the, as rated by us, higher methodological quality of the trials, and includes the only RCT available at present.

a) Phase I/II clinical trial:

Kakkis, et al. Enzyme replacement therapy in mucopolysaccharidosis I. N Engl J Med 2001;344:182-8.

b) Phase III clinical trial:

Wraith, et al. Enzyme replacement therapy for mucopolysaccharidosis I: a randomized, double-blinded, placebo-controlled, multinational study of recombinant human alfa-l-iduronidase (laronidase). J Pediatr 2004;144:581-8.

c) Phase I/II extended clinical trial:

Sifuentes, et al. A follow-op study of MPS I patients treated with laronidase enzyme replacement therapy for 6 years. Mol Genet Metab 2007;90:171-180.

d) 'Less than 5 years study':

Wraith, et al. Enzyme replacement therapy in patients who have mucopolysaccharidosis I and are younger than 5 years: results of a multinational study of recombinant human alfa-l-iduronidase (laronidase). Paediatrics 2007;120(1):e37-46.

e) Phase III extended clinical trial:

Clarke, et al. Long-term efficacy and safety of laronidase in the treatment of mucopolysaccharidosis I. Pediatrics 2009;123:229-240.

f) Dose-optimization trial:

Giugliani, et al. A dose-optimization trial of laronidase (Aldurazyme) in patients with Mucopolysaccharidosis I. Mol Genet Metab 2009;96:13-19.

Additional relevant publications (see also addendum 4 and tables 2 and 3):

g) Cox-Brinkman, et al. Restricted upper extremit

y range of motion in mucopolysaccharidosis type I: no response to one year of enzyme replacement therapy. J Inherit Metab Dis 2007;30:47-50.

h) Arora, et al. Enzyme replacement therapy in 12 patients with MPS

I–H/S with homozygous p.Leu490Pro mutation. J Inherit Metab Dis 2007;30:821.

i) Gabrielli, et al. Enzyme replacement therapy in a 5-month-old boy with attenuated presymptomatic MPS I: 5-year follow-up. Pediatrics 2010;125:e183-e187.

j) Tylki-Szymanska, et al. Anthropometric data of 14 patients with MPS I: retrospective analysis and efficacy of recombinant human alfa-L-iduronidase. Mol Genet Metab 2010;99:10-17.

k) Tylki-Szymanska, et al. Efficacy of recombinant human α-L-iduronidase (laronidase)

on restricted range of motion of upper extremities in mucopolysaccharidosis type I patients. J Inherit Metab Dis (2010) 33:151–157.

l) Grewal, et al. Safety and efficacy of enzyme replacement therapy in combination with hematopoietic stem cell transplantation in Hurler syndrome. Genet Med 2005;7:143-6.

m) Cox-Brinkman, et al. Haematopoietic cell transplantation (HCT) in combination with enzyme replacement therapy (ERT) in patients with Hurler syndrome. Bone Marrow Transplant 2006;38:17-21.

n) Tolar, et al. Combination of enzyme replacement and hematopoietic stem cell transplantation as therapy for Hurler syndrome. Bone Marrow Transplant 2008;41:531-535.

o) Wynn et al. Use of enzyme replacement therapy (Laronidase) before hemaptopoietic stem cell transplantation for Mucopolysaccharidosis I: experience in 18 patients. J Pediatr 2009;154:135-9.

Table 1. Clinical studies on enzyme replacement with laronidase in MPS I patients

First author, **Publication year**	Kakkis, 2001	Wraith, 2004	Sifuentes, 2007	Wraith, 2007	Clarke, 2009	Giugliani, 2009
Study as mentioned in this paper	Study a	Study b	Study c	Study d	Study e	Study f
Study type	Phase 1/2	Phase 3	Phase 1/2 Extension	Under 5 years	Phase 3 Extension	Dose-optimization
Patient number	10	45	5	20	40	33
Phenotype distribution	10% Hurler 80% Hurler-Scheie 10% Scheie	2% Hurler 82% Hurler-Scheie 16% Scheie	80% Hurler-Scheie 20% Scheie	80% Hurler 20% Hurler-Scheie	84% Hurler-Scheie 16% Scheie	30% Hurler 49% Hurler-Scheie 21% Scheie
Mean age at baseline (years)	12.3 Range: 5-22	15.5 Range: 6-43	12.0 Range: 8-17	2.9 Range: 0.5-5.1	15.7 Range: 6.3-43.3	8.9 Range: 1.4-20.7
Intervention (Laronidase)	100 U/kg/week	100 U/kg/week vs. placebo	100 U/kg/week	100 U/kg/week; 4 patients 200 U/kg/week after 26 weeks	100 U/kg/week	100 U/kg/week 200 U/kg/week 200 U/kg/2 wks 300 U/kg/2 wks
Follow-up	52 weeks	26 weeks	5 years	52 weeks	3.5 years	26 weeks
Primary endpoints	Liver/spleen volume Urinary GAG levels	Percent of predicted FVC Distance covered in the 6-MWT	Liver/spleen volume Urinary GAG levels	Urinary GAG levels Liver size Cardiac function	Percent of predicted FVC Distance covered in the 6-MWT	Urinary GAG levels
Secondary endpoints	Joint mobility Growth Apnoea/hypopnoea Cardiac function Functional ability Visual acuity	Liver volume Urinary GAG levels Joint mobility Apnoea/hypopnoea Functional ability	Growth Joint mobility Cardiac function Apnoea/hypopnoea Visual acuity Neurological status Appearance Quality of life	Apnoea/hypopnoea	Liver volume Urinary GAG levels Joint mobility Apnoea/hypopnoea Functional ability Visual acuity Cardiac function Growth	Liver volume Distance covered in the 6-MWT

Table 2. Clinical studies on enzyme replacement with laronidase in MPS I patients

First author, **Publication year**	Cox-Brinkman, 2007	Arora, 2007	Gabrielli, 2009	Tylki-Szymanska, 2010	Tylki-Szymanska, 2010
Study as mentioned in this paper	Study g	Study h	Study i	Study j	Study k
Study type	Single-institutional, prospective cohort trial	Single-institutional, retrospective cohort trial	Case report	Single-institutional, retrospective and prospective cohort trial	Single-institutional, prospective cohort trial
Patient number	6	12	2	14	17
Phenotype distribution	100% Scheie	100% Hurler-Scheie Homozygous p.Leu490Pro	100% Hurler-Scheie	64.3% Hurler 14.3% Hurler-Scheie 21.4% Scheie	59% Hurler 12% Hurler-Scheie 29% Scheie
Mean age at baseline (years)	6.3 Range: 3-11	Median: 8.6 Range: 0.4-23.1	Patient 1: 5 Patient 2: 5 months	4.8 Range: 1-15	8.1 Range: 1-39
Intervention (Laronidase)	100 U/kg/week	100 U/kg/week	100 U/kg/week	100 U/kg/week	100 U/kg/week
Follow-up	52 weeks	Median: 22.5 months Range: 2-71	5 years	Range: 52-260 weeks	Range: 50-208 weeks
Primary endpoints	Range of motion	Urinary GAG levels Hepatosplenomegaly Growth	Urinary GAG levels Hepatosplenomegaly Cardiac function Joint mobility Eye disease Hearing impairment Skeletal disease Growth Development	Height Weight Head circumference Chest circumference	Range of motion Functional status
Secondary endpoints	Functional status			Urinary GAG levels	

Table 3. Clinical studies on enzyme replacement with laronidase prior to HSCT in MPS I

First author, **Publication year**	Grewal, 2005	Cox-Brinkman, 2006	Tolar, 2008	Wynn, 2009
Study as mentioned in this paper	Study l	Study m	Study n	Study o
Study type	Multi-institutional, retrospective case series	Multi-institutional, retrospective cohort study	Single-institutional, prospective trial	Single-institutional, prospective cohort study
Patient number	12	22	7	18
Phenotype distribution	100% Hurler	100% Hurler	100% Hurler	100% Hurler
Age (months)	At initiation of ERT: Median: 12 Range: 8-18	Age at HSCT: Median: 18 Range: 2-39	Age at HSCT: Median: 18 Range: 8-23	Age at HSCT: Mean: 12 Range: 7-24
Intervention (Laronidase)	100 U/kg/week	100 U/kg/week	100 U/kg/week	100 U/kg/week
Duration of pre-HSCT ERT (weeks)	Median: 12 Range: 4-28	Median: 12 Range: 7-24	Range: 11-14	≥ 12
Duration of post-HSCT ERT (weeks)	Median: 7 Range: 3-20	Median: 12 Range: 0-12	8	Until engraftment
Follow-up **(months after HSCT)**	Median: 3 Range: 1-7	Median: 8.5 Range: 3-17.5	Range: 6-29	≥ 6
Primary endpoints	Pulmonary complications associated with HSCT	The 'alive and engrafted rate'	Engraftment Pulmonary complications associated with HSCT	Overall survival Engraftment rate
Secondary endpoints	Donor engraftment Urinary GAG levels	HSCT-associated morbidity	Overall morbidity	HSCT-associated morbidity

3. Therapeutic value

3.1 Beneficial effects of laronidase

3.1.1 Outcome parameters

- Improvement in respiratory function.
  A clinically relevant parameter, since progressive respiratory disease in MPS I leads to shortness of breath, fatigue, daytime somnolence, pulmonary hypertension/cor pulmonale, and increased vulnerability to pulmonary infections. The latter two compose a significant problem and common cause of death in MPS I patients. Improvement of respiratory function is generally quantified by measuring Forced Vital Capacity (FVC) as this parameter can be measured reliably in (older) patients with MPS I, and this parameter is included.
- Improvement in walking ability (e.g. 6-MWT).
  A clinically relevant parameter, since it influences quality of life and 'activities of daily living (ADL)' in MPS I patients.
- Improvement in range of motion.
  A clinically relevant parameter, since improvements in the range of motion may accompany increases in physical activities and quality of life.
- Improvement in growth patterns.
  Anthropometric features of patients with MPS I differ significantly from the healthy population. A major feature of affected patients can be marked dwarfism. This can be a clinically relevant problem for MPS I patients.
- Reduction in hepatomegaly.
  The degree of reduction in hepatomegaly indicates effective clearance of accumulated GAGs in affected patients. In addition, the sometimes significant hepatomegaly can negatively impact respiratory function.
- Improvement in cardiac disease.
  A clinically relevant parameter, since severe cardiac disease (e.g. cardiomyopathy) may lead to early death in MPS I patients.

3.1.2 Motivation for excluding outcome parameters

Urinary GAG-excretion: the degree of reduction in urinary GAG-excretion indicates a biochemical response to ERT, probably consisting of clearance of accumulated GAGs. Urinary excretion of GAGs was used as a primary outcome parameter in several of the most relevant clinical trials. However, the authors

of this review consider the level of urinary excretion of GAGs not as a clinically relevant outcome measurement. To our knowledge, there are no studies demonstrating a correlation between urinary GAG levels and improvement (or deterioration) of clinical signs and symptoms. This relates to the non-specific nature of GAG measurement as well as the fact that urinary GAGs are likely reflective of renal tubular involvement/dysfunction rather than total body disease burden in the MPSs. However, to complete the results of the most relevant clinical trials, the results of the reduction in GAG levels are reported in table 4.a-e and table 5.

More recent studies have shown that the plasma concentration of 'the heparin cofactor II – thrombin complex' may prove to be an import biomarker for monitoring therapeutic efficacy of laronidase in MPS I (Clarke LA, J Inherit Metab Dis, 2011, Jul 6, epub ahead of print). However, more studies, preferably prospective, are needed to establish its true potentials.

3.1.3 Efficacy of laronidase on relevant outcome parameters

Efficacy as deducted from most relevant publications (table 1, see above).

The phase I/II study (open label, 10 patients, table 4.a, see below) showed rapid and significant reductions in liver volume after 52 weeks of treatment. In addition, an increase in height and weight, improvement in range of motion and increase in physical activities, a decrease in the incidence of sleep apnoea and hypopnoea and an improvement in heart function was noted during the study (1).

The extended phase I/II trial, (5 patients, table 4.b, see below) revealed that liver volume further reduced to normal in nearly all patients by 1 year and continued to fall steadily to below the mean normal level over the 6-year period, while various other clinically relevant disease parameters showed further improvement (shoulder range of motion, sleep apnoea as a measure of respiratory function) or remained stable (sleep apnoea in several patients) after six years of treatment. These trends towards improvement (not significant) contrast the natural history of the disease which predicts an ongoing deterioration in all these areas. Although pre-existing heart valve disease did progress in some patients, cardiac disease showed no progression to heart failure (3).

The phase III study (RCT, 45 patients, table 5, see below) showed a statistically significant increase in respiratory function as measured by forced vital capacity. Walking ability as measured by the 6-minute walk test and apnoea-hypopnoea index as a measure of respiratory function improved compared to the placebo group after 26 weeks of treatment. After post-hoc ANCOVA analysis these improvements were significant. In addition, patients receiving laronidase showed a significant reduction in liver volume. In patients with shoulder flexion below the baseline median, a positive trend was noted in patients receiving laronidase (2).

The extended phase III trial (40 patients, table 4.c, see below) showed stabilization or further improvements in most patients with respect to respiratory function, walking ability, liver volume, joint range of motion and quality of life (4).

The phase III study required that patients were capable of performing a reproducible pulmonary function test and 6-minute walk test and therefore excluded patients younger than 5 years of age. Therefore, the

safety and efficacy of laronidase in patients less than 5 years was evaluated in a separate study (5). This 'under 5 years-study' (20 patients, table 4.d, see below) showed improvements in liver volume, left ventricular hypertrophy and apnoea-hypopnoea index. The degree of reduction in hepatomegaly indicated effective clearance of accumulated glycosaminoglycan substrates in young and severely affected patients, consistent with the treatment effect that was observed in older patients.

A dose-optimization study (33 patients, table 4.e, see below) showed no major differences in efficacy between the currently approved laronidase dose and alternative regimens (6). Reduction in liver volume was significant on all tested doses. Mean improvement in walking ability (as measured by the 6 minute walk test) was not significant in this 26-weeks study.

Efficacy as deducted from the additional relevant publications (tables 2 & 3, see above).
A 12-months study in six attenuated MPS I patients failed to show significant improvement in large joint range of motion at different time intervals (18). However, from other studies (e.g. the phase III extension study) it has become clear that it takes longer for some of the effects of laronidase to become apparent. In addition, a more recent study on the effectiveness of laronidase on the range of motion of upper extremities of patients with MPS I shows that introduction of ERT led to slower progression of symptoms, especially in the passive range of motion in all patients (19).

Another study, a cohort of 14 Hurler-Scheie patients homozygous for the p.Leu490Pro missense mutation, showed a clear improvement in liver- and spleenvolume after 24 months of treatment, however, no clear conclusions could be drawn with regard to the efficacy of ERT for growth (20). In a more recent study, no effect of laronidase on growth patterns of MPS I patients was shown, even after 104-260 weeks of treatment (21).

A case-report on the 5-year follow-up of an initially asymptomatic boy with attenuated MPS I in whom laronidase was started from the age of 5 months compares his clinical course to that of his older sister, who began treatment at 5 years of age. A comparison of the clinical features in these children at the age of approximately 5 years provides compelling evidence that early ERT might prevent the development of major clinical features of MPS I (17).

Use of ERT prior to HSCT has been shown to be safe in a limited number of trials (7-10) and has the potential to improve the clinical condition of patients before the HSCT procedure, which may improve HSCT-related morbidity and mortality (9,10).

Tables 4.a. – 4.e. and table 5 show the results of laronidase on the most relevant clinical parameters.

Table 4.a. Efficacy of laronidase in MPS I patients, after 52 weeks of treatment [1]

N/A: not available or not applicable

* In six prepubertal patients

	[laronidase] *(n = 10)*	*p*
Primary endpoints	Mean decrease in liver volume 25%	<0.001
	Mean reduction in urinary GAG levels 63%	<0.001
Secondary endpoints	Mean increase in rate of height growth 85%*	0.01
	Mean decrease in shoulder restriction (R) 28°	< 0.001
	Mean decrease in shoulder restriction (L) 26°	0.002
	Cardiac function improved in all patients	0.002
	Decrease in AHI 61%	N/A
	Functional ability improved in all patients	N/A

Table 4.b. Efficacy of laronidase in MPS I patients, after 6 years of treatment [3]

N/A: not available or not applicable

	[laronidase] *(n = 5)*	*p*
Primary endpoints	Mean reduction in liver volume > 20%	<0.0001
	Mean reduction in urinary GAG levels 77%	0.0004
Secondary endpoints	Mean increase in height 27%	N/A
	Mean increase in shoulder flexion (R) 33.2°	N/A
	Mean increase in shoulder flexion (L) 25.0 °	N/A
	Cardiac function improved in 80% of patients	0.1250
	Decrease in AHI in 80% of patients	N/A
	Functional ability improved in all patients	N/A

Table 4.c. Efficacy of laronidase in MPS I patients, after 3.5-4 years of treatment [4][1]

[1] No p-values reported. However, the proportion of patients whose clinical status improved, remained stable, or declined over the course of the trial was determined by using specific predefined thresholds (see article) (2).

	[laronidase] *(n = 40)*	*Results*
Primary endpoints	Mean decline in FVC 0.78% per year	73% improved or stable
	Mean improvement in 6-MWT 17.1 m	78% improved or stable
Secondary endpoints	Mean reduction in urinary GAG levels 72%	72% ≤ + 2 SD of normal
	Mean decrease in liver volume 38%	95% within normal values
	Mean increase in shoulder flexion 17.4 °	95% improved or stable
	Mean reduction in AHI 4.4 events per h	94% improved or stable
	Mean improvement in disability index 0.31	77% improved or stable
	Median height velocity	normalized in all pediatric patients

Table 4.d. Efficacy of laronidase in MPS I patients < 5 years, after 52 weeks of treatment [5]

N/A: not available or not applicable

* In patients with clinically significant abnormal baseline values

	[laronidase] *(n = 20)*	*Results*
Primary endpoints	Mean decrease in liver edge 69.5%	50% within normal values
	Mean reduction in urinary GAG levels 61.3%	N/A
	Mean decrease in cardiac z-score 11.3%	N/A
Secondary endpoints	Mean decrease in AHI 8.5%*	clinically significant in 33%

Table 4.e. Results of a dose-optimization study on laronidase in MPS I patients, after 26 weeks of treatment [6]

	[laronidase] *(n = 33)*	*95% CI*
Primary endpoints	Mean reduction in urinary GAG levels (100 IU/kg/wk) 58%	[42,73%]
	Mean reduction in urinary GAG levels (200 IU/kg/wk) 66%	[54,80%]
	Mean reduction in urinary GAG levels (200 IU/kg/2wks) 66%	[59,73%]
	Mean reduction in urinary GAG levels (300 IU/kg/2wks) 63%	[58,68%]
Secondary endpoints	Mean decrease in liver volume (100 IU/kg/week) 26%	[19,34%]
	Mean decrease in liver volume (200 IU/kg/week) 31%	[23,38%]
	Mean decrease in liver volume (200 IU/kg/2wks) 31%	[15,46%]
	Mean decrease in liver volume (300 IU/kg/2wks) 32%	[24,41%]
	Mean change in 6-MWT (100 IU/kg/week) + 7m	[-80,94]
	Mean change in 6-MWT (200 IU/kg/week) -12 m	[-73,49]
	Mean change in 6-MWT (200 IU/kg/2wks) + 25 m	[-44,95]
	Mean change in 6-MWT (300 IU/kg/2wks) + 52 m	[-15,119]

Table 5. Efficacy of laronidase in MPS I patients, after 26 weeks of treatment; a randomized controlled trial [2]

N/A: not available or not applicable

	[laronidase] *(n = 22)*	*[placebo]* *(n = 23)*	*Mean difference* *(p)*
primary endpoints			
- Mean improvement in FVC	4.9%	-0.7%	5.6% (median 3.0; p=0.009)
- Mean change in 6-MWT	19.7 m	-18.4 m	38.1m (median 38.5; p=0.066)
secondary endpoints			
- Mean change in urinary GAG levels	- 54.1%	+47.3%	101.4% (< 0.001)
- Mean change in liver volume	-18.9%	+1.3%	20.2% (0.001)

- Mean change in AHI	N/A	N/A	3.6 events per h (0.145)
- Mean change in shoulder flexion	+9.6°	-4.8°	14.4° (not significant)

3.2 Adverse effects of laronidase

Adverse effects consist mainly of 'infusion associated reaction' (IAR's), which are hypersensitivity reactions (IgG mediated) to the intravenous enzyme. Symptoms usually resolve after the infusion is stopped. The incidence of infusion reactions appears to decrease with time. Treatment of patients showing infusion associated reactions could be continued by reducing the rate of infusion and by the use of prophylactic drugs (antihistamines/antipyretics), administered approximately 60 minutes prior to the start of the infusion. Patient with an acute underlying illness at the time of laronidase infusion appear to be at greater risk for IAR's.

Reporting on IAR's in the most relevant studies:

- Kakkis et al, 2001: five (of 10) patients had transient urticaria during infusions. In three (of 10) patients, urticaria was accompanied by angioedema and by moderate transient hypoxemia. One (of 10) patient had fever, chills and 'fussy behavior'.
- Wraith et al, 2004: Infusion-related reactions consisted mainly of flushing, fever, headache and rash and had a similar patient incidence in the Laronidase and placebo groups (32% vs 48%). Most reactions were mild. No medical intervention or interruption of infusion was required.
- Sifuentes et al, 2007: only one adverse event (mild abdominal pain) met the reporting criteria as defined in the study protocol.
- Wraith et al, 2007: all patients experienced at least one adverse event. The majority of these were related to the underlying disease. Most commonly reported adverse events: pyrexia, diarrhoea, vomiting, cough, rhinorrhea, rhinitis, and rash (> 50%).
- Clarke et al, 2009: adverse events related to treatment were reported in 67% of patients. Adverse events that occurred in at least 10% of patients were: rash (22%), arthralgia (20%), headache (18%), flushing (16%), injection site reaction (13%), arthropathy (11%), abdominal pain (11%), back pain (11%), fever (13%), skeletal pain (11%) and nausea (11%). Serious adverse events occurred in two patients: hypotension and vomiting and respiratory difficulty and anaphylaxis.
- Giugliani et al, 2009: Drug-related adverse events were reported in 61% of patients. Patients in the

lowest dose group had the lowest rate of adverse events. Adverse events consisted mainly of pyrexia (21%), vomiting (15%), rash (15%), and urticaria (12%). One death due to respiratory failure was reported. Although the event was assessed unlikely related to treatment with laronidase, a possible causal relationship could not be ruled out.

Adverse drug events reported during the phase III-study and its extension (2,4) in a total of 45 patients age 5 years and older and treated up to 4 years are listed below using the following categories of frequency: very common (≥ 1/10); common (≥ 1/100 to < 1/10). Due to the small patient population, an adverse drug event reported in a single patient is classified as common (EMA-Summary of Product Characteristics).

MedDRA System Organ Class	**MedDRA Preferred Term**	**Frequency**
Investigations	Body temperature increased, oxygen saturation decreased	Common
Cardiac disorders	Tachycardia	Common
Nervous system disorders	Headache	Very common
	Paraesthesia, dizziness	Common
Respiratory, thoracic and mediastinal disorders	Respiratory distress, dyspnoea, cough	Common
Gastrointestinal disorders	Nausea, abdominal pain	Very common
	Vomiting, diarrhoea	Common
Skin and subcutaneous tissue disorders	Rash	Very common
	Angioneurotic edema, swelling face, urticaria, pruritus, cold sweat, alopecia, hyperhidrosis	Common
Musculoskeletal and connective tissue disorders	Arthropathy, arthralgia, back pain, pain in extremity	Very common
	Musculoskeletal pain	Common
Vascular disorders	Flushing	Very common
	Hypotension, pallor, peripheral coldness	Common
General disorders and administration site conditions	Pyrexia, infusion site reaction	Very common
	Chills, feeling hot, feeling cold, fatigue, influenza like illness	Common
Immune system disorders	Anaphylactic reaction	Common
Psychiatric disorders	Restlessness	Common

Adverse drug events to laronidase reported during during a prospective, open-label study in a total of 20 patients under 5 years of age and mainly of the severe phenotype, treated up to 12 months (5) are listed

below. Adverse drug events were all mild to moderate in severity (EMA-Summary of Product Characteristics).

MedDRA System Organ Class	**MedDRA Preferred term**	**Frequency**
Investigations	blood pressure increased	Very common
	oxygen saturation decreased	Very common
Cardiac disorders	tachycardia	Very common
General disorders and administration site conditions	pyrexia	Very common
	chills	Very common

Table 6. Adverse reactions (EMA-summary of product characteristics)

Most frequent	Headache, nausea, abdominal pain, rash, arthralgia, backpain, pain at extremity, flushing, pyrexia, infusion site reactions, blood pressure increased, oxygen saturation decreased, tachycardia and chills.
Serious	Anaphylaxis, facial oedema, respiratory insufficiency

3.3 Experience with laronidase

Dutch experience with laronidase is limited. Although laronidase has been available for 7 years, exposure has been less than 20,000 patient-years. This is due to the rarity of the disease (3). However, for this review we decided to present the complete experience with laronidase in the Netherlands (*see **addendum1***). Since the introduction of laronidase in the Netherlands 47 patients have been evaluated for treatment at one of the two 'centers of expertise' on lysosomal storage disorders: the Erasmus Medical Center (Rotterdam) and the Academic Medical Center (Amsterdam).These two centers are the only ones prescribing laronidase in the Netherlands. HSCT for MPS I in the Netherlands is performed in the UMC Utrecht.

In the Netherlands, 20 MPS I patients are currently being treated with laronidase and are carefully supervised by experienced specialists from these two 'centers of expertise'. Ten patients have been treated with laronidase during a short term prior to HSCT (ranging from 1.5-8 months). Four patients who received laronidase as chronic treatment have died. One patient initiated on chronic laronidase treatment decided to stop treatment because this patient felt that the potential benefits of laronidase did not outweigh the burden of chronic intravenous treatment. Finally, 11 patients were not started on laronidase. Five of them received a HSCT, and no indication for laronidase prior to HSCT was present. The other 6 patients were not started on laronidase because of various and individual reasons.

In all 47 patients a careful evaluation was performed in the 'centers of expertise', in order to decide whether the patient should start with laronidase treatment. Factors relevant decision making were, amongst others, severity of the disease, the possibility for a HSCT, and expected compliance to chronic intravenous therapy.

The relatively small and heterogeneous cohort precludes clear evaluation of efficacy data in the Dutch cohort. To monitor therapeutic efficacy in this group of patients, it will be crucial to continue the current high quality data collection in all patients, in order to allow future analyses of data (addendum 5). No MPS I patients have been withdrawn from treatment with laronidase because of serious adverse events in the Netherlands.

Table 7. Dutch experience with laronidase

	laronidase
beperkt: < 3 jaar op de markt of < 100.000 voorschriften (niet-chronische indicatie)/20.000 patiëntjaren (chronische medicatie)	**X**
voldoende: ≥ 3 jaar op de markt, en > 100.000 voorschriften/20.000 patiëntjaren	
ruim: > 10 jaar op de markt	

*Bron: CFH-criteria voor beoordeling therapeutische waarde; www.fk.cvz.nl.

3.4 Applicability

Clinical trials and additional studies, although all limited in number of included patients and complex to interpret due to the range of phenotypic disease severity of the included patients, have demonstrated that ERT is safe and has clinically relevant efficacy in patients with MPS I, across a wide range of ages (young children to adults) and phenotypes (severe and attenuated).
Apart from pregnancy and lactation on which there are insufficient data, and severe hypersensivity (e.g. anaphylactic reaction) to the active substance or to any of the excipients, there are no contra-indications for the use of laronidase in MPS I patients.
Laronidase should not be administered simultaneously with chloroquine or procaine due to the potential risk of interference with the intracellular uptake of laronidase.

3.5 Ease of use

Laronidase is administered once every week by intravenous infusion. Patients with a body weight of 20 kg or less should receive a total volume of 100 ml of sodium chloride 9 mg/ml (0.9%) solution for infusion. Patients with a body weight greater than 20 kg should receive a total volume of 250 ml. The initial infusion rate of 2 U/kg/h may be incrementally increased every fifteen minutes, if tolerated, to a maximum of 43 U/kg/h. The entire infusion volume should be delivered over approximately 3 to 4 hours, and ranges from 2 to > 5 hours in the Netherlands (including time for preparation; see *addendum 2*). Pre-treatment with antihistamines and/or antipyretics, should be considered in patients with persistent or severe infusion associated reactions.

Laronidase can be administered at home or even at school or at work if during a period of approximately 6 months no serious infusion associated reactions or other side effects have been observed (22). Home therapy is considered to be less stressful and more convenient than hospital-based therapy. Patients do

not necessarily have to miss school or work on the day they receive treatment. Home therapy may therefore improve both compliance with treatment with laronidase as well as quality of life of patients. Indeed, most Dutch patients currently receive laronidase in their home. Home treatment is primarily performed by home treatment teams ('thuiszorg'), but also by the partner of the patients or the patients him- or herself (see addendum 2). An emergency protocol is provided in (the unlikely) case adverse events occur at home. Patients adhere well to the prescribed dosing regimens and ease of use should be judged in relation to the perceived effectiveness and the severity of the disorder. See *addendum 2* for more information on this from the Dutch MPS I patients on laronidase.

Table 8. Laronidase

Administration	Intravenously
Frequency	Once weekly

4. Conclusions

Conclusions and claims

Mucopolysaccharidosis type I (MPS I) is an ultra-rare (± 1 : 125,000 life births) lysosomal storage disorder and is caused by a deficiency of the lysosomal enzyme α-L-iduronidase. The clinical spectrum of the disease is very broad, ranging from a severe to attenuated phenotype. Regardless of the phenotype, however, MPS I is always a severe, debilitating and potentially life-threatening disease.
Recombinant α-L-iduronidase (laronidase, Aldurazyme®) is the only EMA- and FDA-approved treatment option for MPS I patients, and is indicated for the (long term) treatment of the non-neurological manifestations of the disease in all MPS I patients.
The CFH concluded in 2003 that, based on the limited available scientific evidence, treatment with laronidase showed reduction in urinary GAG-excretion, liver volume, pulmonary function and walking distance of MPS I patients. In addition, the CFH concluded that the available evidence was too limited to draw firm conclusions on the therapeutic value of laronidase and that further research on the safety and efficacy of laronidase was needed (CFH-report 03/15, July 10, 2003). The authors of this review have the opinion that laronidase treatment has significant and relevant therapeutic value for selected groups of MPS I patients, based on the previously and more recently available literature (A2, B & C level of evidence), as well as on their own experiences with over 11 years of laronidase treatment in MPS I (type D level of evidence; *expert opinion*).

To date, 108 patients with MPS I have been studied within the scope of prospective trials on efficacy of laronidase: 10 patients in the phase I/II trial, 45 patients in the (randomized, placebo controlled) phase III trial, 20 patients in an open labelled study on safety and efficacy in patients < 5 years and finally 33 patients in an open labelled dose-optimization trial (table 1). Five of the 10 patients in the phase I/II and 40 of the 45 patients in the phase III study were subsequently studied in long term extension studies.
In addition, 51 MPS I patients were studied in 5 open label, single centre, prospective or retrospective case cohort studies on therapeutic efficacy (table 2).
Finally, 59 patients were included in analyses on the safety and efficacy of laronidase prior to HSCT in patients with the severe Hurler phenotype of MPS I (table 3).
All studies in MPS I are hampered by a very small number of included patients, due to its ultra low prevalence, the extremely broad phenotypic spectrum of the disease with huge differences in severity and rate of progression between the different phenotypes, and the lack of biomarkers (correlating with disease severity and efficacy of therapy on clinically relevant parameters).
Despite these severe restrictions, the following conclusions can be drawn:
Efficacy of treatment with laronidase on the 6 clinically relevant outcome parameters (improvements in respiratory function, walking ability, joint range of motion, growth patterns, cardiac disease and reduction in liver volume; see 3.1.1) is demonstrated by the most relevant clinical trials (table 1 and tables 4.a – 4e and table 5) and by the additional clinical studies (table 2).
Statistically significant improvement in liver volume and respiratory functions (lung function (FVC) and Apnea-Hypopnea index (AHI)) were observed in the only RCT performed with laronidase (2). Stabilization and improvement of joint range of motion, walking ability (6 minute walk test), growth and cardiac function was observed in the open labelled studies in many patients (1,3-5). As the natural course in MPS I is characterized by a continuous progressive deterioration of clinical signs and symptoms, stabilization of disease parameters on laronidase is considered to demonstrate efficacy. In the phase III extension study (40 patients) improvement or stabilization of pulmonary function (AHI and FVC), 6 minute walk test, joint range of motion and disability index was documented (4). Stabilization and slow improvement of relevant parameters was also observed in other small open-label single-centre studies (18-21).
Several studies have demonstrated that laronidase treatment in patients with the severe Hurler phenotype waiting for a HSCT procedure may improve the pre-transplant condition (7-10).

Laronidase treatment has proven to be safe. Side effects are restricted to infusion associated reactions which respond to pre-treatment with antihistamines/antipyretics and generally subside during prolonged treatment (1-6). In addition, laronidase before HSCT does not negatively influence engraftment or outcome of HSCT (9,10).

Laronidase has been studied in all age groups and in all phenotypes. There is (inter-) national consensus on the place of laronidase in the treatment of MPS I: laronidase is indicated for all patients with MPS I who did not have had a successful HSCT or do not qualify for HSCT.

Experience with laronidase in the Netherlands is limited due to the extreme rarity of the disorder. Data

collected on all Dutch patients are presented in this review (***addendum1)***, and demonstrate that the number of patients on laronidase has remained stable and is lower than the previously estimated number of 25 (CFH-report 03/15, July 10, 2003). The cost of laronidase treatment in the Netherlands is therefore also significantly lower than predicted.

Laronidase is administered by weekly (approximately 3 – 4 hr) infusions. This 'ease of use' needs to be balanced against the severity of the disease and the relentless deterioration without treatment. Compliance is very high and to the experience of the Dutch patients the burden of chronic invasive treatment is outweighted by the perceived efficacy (*see* ***addendum2***).

A MPS I Registry (www.MPSIregistry.com) was established by BioMarin Pharmaceutical (Novato, CA) and Genzyme (Cambridge, MA) as a post-marketing, observational database designed to capture clinical data of MPS I patients for characterization of the natural course of the disease and future evaluation of the long-term safety and efficacy of ERT. The captured data focus on patient demographic and disease profiles, clinical assessment data (clinical signs and symptoms of MPS I), and patient treatment status. As of May 6 2011, data from 987 patients with MPS I have been collected from physicians in over 33 countries. Of them, 522 (45%) received laronidase and no HSCT (laronidase as chronic treatment); 142 (14%) received both laronidase and HSCT, 203 (20%) received only HSCT and finally 120 (12%) received neither laronidase nor HSCT. The voluntary and observational nature of this registry has, until now, precluded reliable analysis of the data for assessment of therapeutic efficacy of laronidase.
A recent study (Verhulst K., submitted for publication) indicate an overall low source-to-database error rate in the MPS I Registry in two different substudies (2.7% (47 discrepancies out of 1715 items ; 95% confidence interval [CI] [2.2%, 3.5%]) in study 1 and 3.7% (64 discrepancies out of 1732 items; 95% CI [2.9%, 4.7%]) in study 2). In addition, no systematic errors were found. However, data on relevant outcome parameters for assessment of the therapeutic value of laronidase are not documented in the registry in a protocolized way or even not at all, again as a result of the voluntary observational nature of the data capturing. As a result, the registry, as it is, cannot be used to extract reliable data on therapeutic value of laronidase. Only future studies, using truly prospective, protocolized and focused, data procurement and entry will allow for such studies. It is debatable if this can and should be done by means of the MPS I Registry.

A methodological robust assessment of therapeutic efficacy of laronidase by studying the data collected by the two Dutch treatment centers for patients with MPS I (AMC and ErasmusMc) is not feasible due to the small number of patients in combination with the phenotypic heterogeneity of these patients. In addition, reliable longitudinal data from patients with MPS I who were not treated by laronidase are lacking, precluding a controlled study. Probably, only an international, multi-center, long-term, controlled study may lead to new data on therapeutic value of laronidase in MPS I. In addition, the use of the newly discovered potential biomarker in MPS I (the heparin cofactor II-thrombin complex) may help in future studies on therapeutic efficacy of laronidase, but further studies are needed to demonstrate its value.

In conclusion, despite the small number of patients studied and the complexity of the disorder with a broad range of phenotypic severity characterized by different rates of disease progression, trials and additional studies have shown clear benefit of treatment with laronidase on clinically relevant outcome parameters. Laronidase is indicated for all MPS I patients who do not qualify for HSCT or did not receive HSCT. Given the extreme complexity of the disease and invasiveness of the treatment, the use of laronidase should be limited to expert centers on lysosomal storage disorders, including MPS I. These expert centers should have a multi-disciplinary approach to the care for and treatment of these patients. Currently, there are two centers for lysosomal storage disorders in the Netherlands (Erasmus Medical Center, Rotterdam and the Academic Medical Center, Amsterdam) that fully qualify as expert centers for treatment of MPS I patients. These centers will continuously collect data on natural course and treatment of the MPS I patients in the Netherlands.

There are several important issues that need further exploration to determine the role of laronidase in the treatment of MPS I more precisely. These issues are specified in ***addendum 5*** (issues to explore; 'witte vlekken analyse'). The two Dutch 'centers of expertise' will take part in several of these studies.

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Addenda

1. Addendum 1: Overview of number of patients on laronidase and costs of laronidase treatment.
2. Addendum 2: MPS I Questionnaire Dutch patients with MPS I (survey by the Dutch Society for patients with inborn errors of metabolism).
3. Addendum 3: participants of the European Consensus Meeting on ERT and/or HSCT in MPS I, Amsterdam, September 28, 2010.
4. Addendum 4: relevant articles regarding treatment of MPS I with laronidase.
5. Addendum 5: issues to explore ('witte vlekken analyse').
6. Addendum 6: relevant biographies of participants in this review (on request by ZonMw).

Addendum 1: Overview of number of patients on laronidase and costs of laronidase treatment in the Netherlands

Year	Number of patients treated short term (prior to HSCT) with laronidase	Number of patients on chronic (long term) laronidase treatment	Number of vials used per year	Total costs per year Excl btw	Incl btw
2006	0	17	6823	€ 4.776.100,00	€ 5.062.666,00
2007	4	20	7011	€ 4.907.700,00	€ 5.202.162,00
2008	0	21	6838	€ 4.786.600,00	€ 5.073.796,00
2009	1	21	7733	€ 5.413.100,00	€ 5.737.886,00
2010	1	20	8024	€ 5.616.659,43	€ 5.953.659,00



Verslag van enquête onder MPS I patiënten die Laronidase (Aldurazyme®) gebruiken

Uitgevoerd tussen 15-10-2010 en 30-10-2010

Auteur: H.K. Meutgeert-Dekker

Inleiding:

In een samenwerking tussen WKZ/UMC Utrecht, Erasmus MC en AMC, wordt voor ZonMw dit najaar een review gedaan van de opname van Laronidase in de beleidsregel weesgeneesmiddelen. Om het gebruikersperspectief toe te lichten, is VKS gevraagd hieraan bij te dragen. Dit hebben wij gedaan, door een klein onderzoek op te zetten onder alle gebruikers van Laronidase in Nederland, die het middel op dit moment nog gebruiken. Niet ondervraagd zijn patiënten en ouders, die slechts voor korte tijd gebruik maken van Laronidase, bijvoorbeeld voorafgaande aan het ondergaan van een stamceltransplantatie.

Volgens opgave van de betrokken UMC's ontvangen op dit moment 17 patiënten in Nederland langer durend Laronidase . In totaal hebben 14 van deze patiënten aan ons onderzoek meegewerkt (82%)

Doel:

Met de korte vragenlijst, willen wij nadrukkelijk het perspectief van de patiënt inbrengen, bij de behandeling van een zeldzaam ziektebeeld met een zeer heterogene presentatie. Door de zeldzaamheid van het ziektebeeld is het moeilijk om met de gebruikelijke methodes betrouwbare gegevens te genereren over effectiviteit en werkzaamheid.

Methode:

De vragenlijst omvat zeven vragen en is afgestemd met de betrokken specialisten in de UMC's. Tien patiënten komen uit het ledenbestand van VKS. Vier patiënten werden met medewerking van het AMC benaderd. In de periode van 15-10 tot 30-10 zijn alle patiënten die te achterhalen waren en die mee wilden werken, telefonisch benaderd door een medewerker van VKS. Deze medewerker is verder niet betrokken bij de review en heeft geen specifieke kennis van de ziekte MPS I. Gesproken werd met zeven vaders van patiënten, vier moeders van patiënten en drie patiënten zelf. De vragenlijsten zijn anoniem verwerkt in een Excel-spreadsheet

Resultaat:

Uit bijgaande verwerking van de vragenlijsten wordt duidelijk dat het merendeel van de patiënten ervaart dat het gebruik van Laronidase hun kwaliteit van leven veel verbetert en dat de behandeling veel effect heeft op de verschijnselen van de ziekte MPS I.

1. Hoe lang wordt u (uw kind) al behandeld met Aldurazyme			
Minder dan één jaar	Tussen de één en drie jaar	Tussen de drie en vijf jaar	Langer dan vijf jaar
0	3 (21%)	5 (36%)	6 (43%)



2. Hoeveel tijd kost een infusie u, wekelijks, inclusief het ophalen, voorbereiden, inlopen en het aanprikken van het infuus?			
Tussen de twee en drie uur	tussen de drie en vier uur	tussen de vier en vijf uur	meer dan vijf uur
1 (7%)	4 (29%)	5 (36%)	4 (29%)



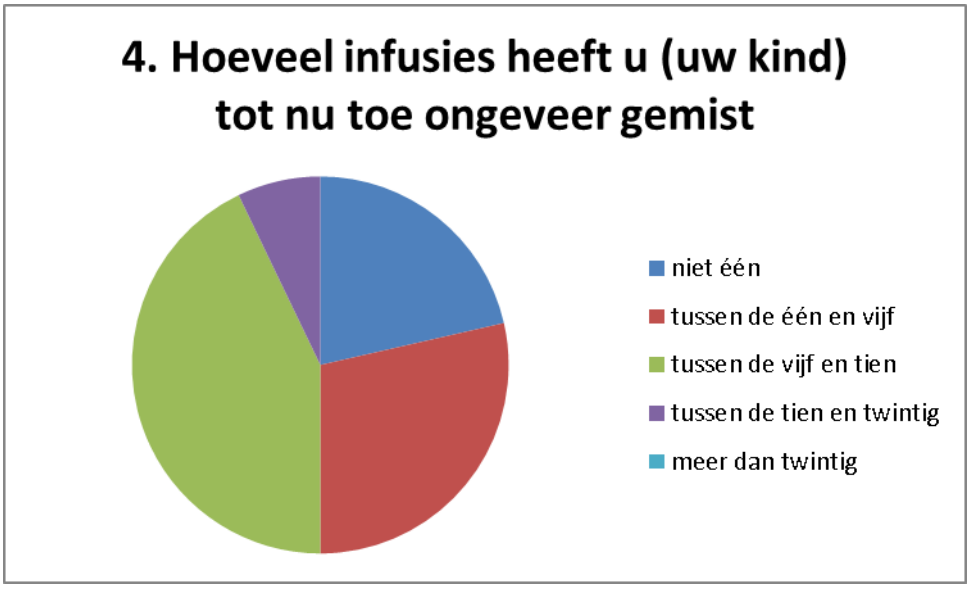
3a. welke hulpverlener helpt bij het aanprikken			
zelf	specialist ziekenhuis	thuiszorg	partner
1 (7%)	4 (29%)	8 (57%)	1 (7%)



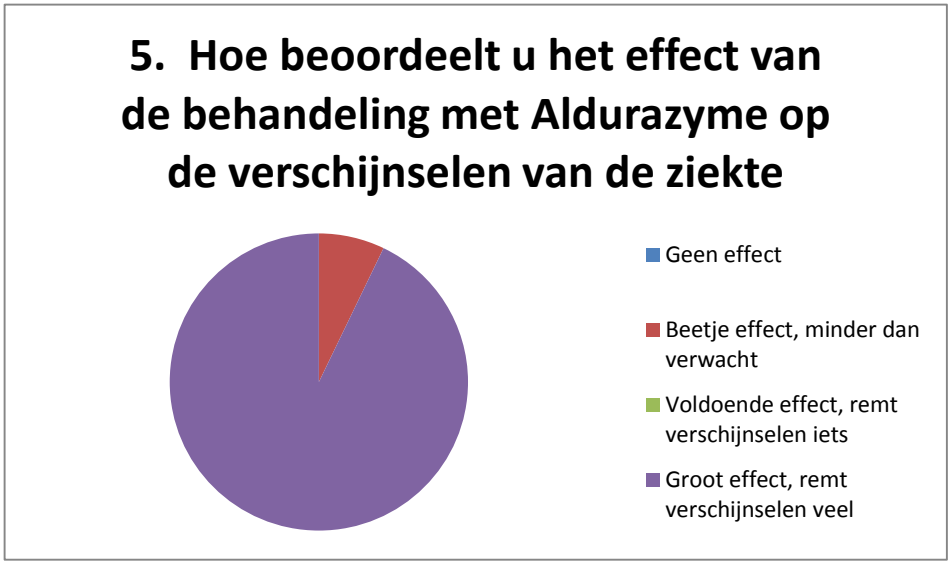
3b hoeveel tijd heeft hij/zij daar per week voor?				
Tussen de twee en drie uur	tussen de drie en vier uur	tussen de vier en vijf uur	meer dan vijf uur	geen idee/nvt
4 (29%)	0	3 (21%)	5 (36%)	2(14%)



4. Hoeveel infusies heeft u (uw kind) tot nu toe ongeveer gemist				
niet één	tussen de één en vijf	tussen de vijf en tien	tussen de tien en twintig	meer dan twintig
3 (21%)	4 (29%)	6 (43%)	1(7%)	0

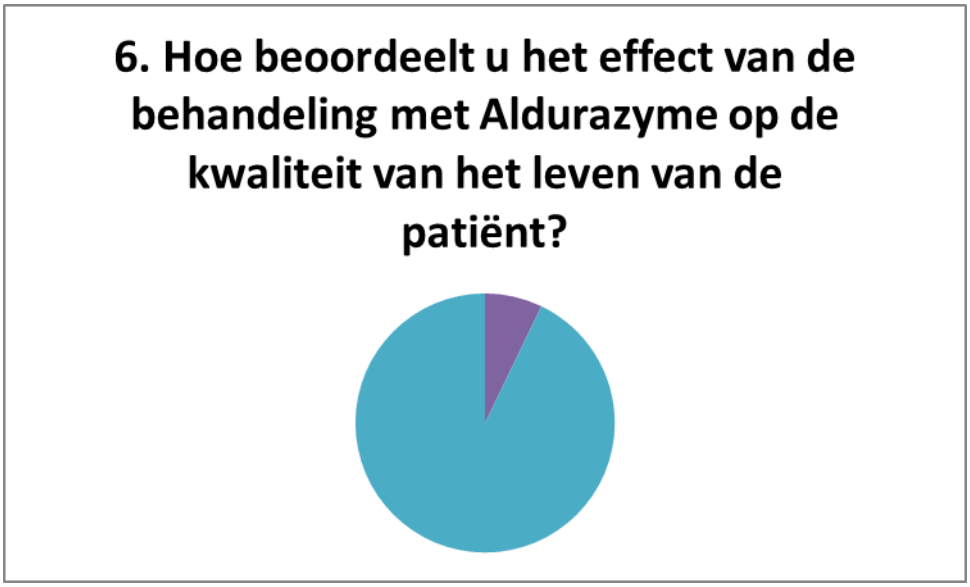


5. Hoe beoordeelt u het effect van de behandeling met Aldurazyme op de verschijnselen van de ziekte			
Geen effect	Beetje effect, minder dan verwacht	Voldoende effect, remt verschijnselen iets	Groot effect, remt verschijnselen veel
0	1 (7%)	0	13 (93%)



6. Hoe beoordeelt u het effect van de behandeling met Aldurazyme op de kwaliteit van het leven van de patiënt?

Kwaliteit van leven neemt af door de frequente infusen	Kwaliteit van leven neemt af door onvoldoende werking van het middel en bijwerkingen	Kwaliteit van leven blijft min of meer gelijk	Kwaliteit van leven is iets toegenomen, zonder behandeling was het slechter geweest	Kwaliteit van leven is duidelijk verbetert ten opzichte van de periode voor de behandeling of ten opzichte van de verwachtingen
0	**0**	**0**	**1 (7%)**	**13 (93%)**



7. Kunt u in één zin aangeven of u het gebruik van Aldurazyme wel of niet de moeite waard vindt en waarom?

Allen: Wél de moeite waard want…

durft het risico niet te nemen het middel niet te gebruiken (2 x)
effecten zijn duidelijk te zien en te merken
fantastisch wondermiddel, heel fijn leven nu.
het doe iets in mijn lijf, of het gesmeerd wordt, veel losser
kunnen niet leven zonder dit middel, heel belangrijk (2x)
kwaliteit van leven stukken beter, voelt zich met medicijnen stukken beter (5x)
organen stabiel, rugklachten, mobiliteit
zonder Aldurazyme in een rolstoel

ID-nummer patiënt …….

Vragenformulier gebruikers Aldurazyme (of hun ouders)

Vragenlijst telefonisch afgenomen door……. ……. op ……Gesproken met (vader/moeder/patient)

1. Hoe lang wordt u (uw kind) al behandeld met Aldurazyme

1 – Minder dan één jaar

2 – Tussen de één en drie jaar

3 – Tussen de drie en vijf jaar

4 – Langer dan vijf jaar

2. Hoeveel tijd kost een infusie u, wekelijks, inclusief het ophalen, voorbereiden, inlopen en het aanprikken van het infuus?

1 – Tussen de twee en drie uur

2 – tussen de drie en vier uur

3 – tussen de vier en vijf uur

4 – meer dan vijf uur

3. Welke hulpverlener helpt bij het aanprikken en de verzorging en hoeveel tijd heeft hij/zij daar per week voor?

Hulpverlener: ……Thuiszorg/ wijkverpleging/ PGB/ huisarts/specialist in ziekenhuis

Tijd: 1 – Tussen de twee en drie uur

2 – tussen de drie en vier uur

3 – tussen de vier en vijf uur

4 – meer dan vijf uur

4. Hoeveel infusies heeft u (uw kind) tot nu toe ongeveer gemist

1 – niet één

2 – tussen de één en vijf

3 – tussen de vijf en tien

4 – tussen de tien en twintig

5 – meer dan twintig

5. Hoe beoordeelt u het effect van de behandeling met Aldurazyme op de verschijnselen van de ziekte

1 – Geen effect

2 – Beetje effect, minder dan verwacht

3 - Voldoende effect, remt verschijnselen iets

4 – Groot effect, remt verschijnselen veel

6. Hoe beoordeelt u het effect van de behandeling met Aldurazyme op de kwaliteit van het leven van de patiënt?

1 – Kwaliteit van leven neemt af door de frequente infusen

2 – Kwaliteit van leven neemt af door onvoldoende werking van het middel en bijwerkingen

3 – Kwaliteit van leven blijft min of meer gelijk,

4 – Kwaliteit van leven is iets toegenomen, zonder behandeling was het slechter geweest

5 – Kwaliteit van leven is duidelijk verbetert ten opzichte van de periode voor de behandeling of ten opzichte van de verwachtingen.

7. Kunt u in één zin aangeven of u het gebruik van Aldurazyme wel of niet de moeite waard vindt en waarom?

Wel/Niet de moeite waard want……

……
……

Addendum 3

Participants in the European expert consensus meeting process on ERT and/or HSCT in MPS I, Amsterdam.

Meeting: 28 september 2010, Amsterdam Schiphol Airport

Boelens JJ[1], Das AM[2], Jones S[3], Mahlaoui N[4], Mengel E[5], O'Meara A[6], Parini R[7], Rovelli A[8], Scarpa M[9], Sykora KW[10], Valayannopoulos V[11], Vellodi A[12], Veys P[13], Wijburg FA[14], Wynn RF[15]

[1] Department of Pediatrics: Pediatric Blood and Marrow Transplantation Program, University Medical Center Utrecht, Utrecht, Netherlands; [2] Department of Pediatric Metabolic Medicine, Hannover Medical School, Hannover, Germany; [3] Department of Pediatric Metabolic Diseases, Royal Manchester Children's Hospital, Manchester, United Kingdom; [4] Pediatric Immunology-Hematology Unit, Necker-Enfants Malades Hospital, Paris, France; [5] Department of Pediatric Metabolic Diseases, Children's Hospital, University of Mainz, Mainz, Germany; [6] Department of Haematology/Oncology, Our Lady's Children's Hospital, Dublin, Ireland; [7] Rare Metabolic Diseases Unit, Department of Pediatrics, San Gerardo Hospital, Monza, Italy; [8] Bone Marrow Transplant Unit, Department of Pediatrics, San Gerardo Hospital, Monza, Italy; [9] Department of Pediatric Metabolic Diseases, University of Padova, Padova, Italy; [10] Bone Marrow Transplant Department, Department of Pediatrics, Medical School Hannover, Hannover, Germany; [11] Reference Center for Inherited Metabolic Disorders, Necker-Enfants Malades Hospital, 75015 Paris, France; [12] Department of Pediatric Metabolic Diseases, Great Ormond Street Hospital for Children NHS Trust, London, United Kingdom; [13] Department of Bone Marrow Transplantation, Great Ormond Street Hospital for Children NHS Trust, London, United Kingdom; [14] Department of Pediatrics and Amsterdam Lysosome Center "Sphinx," Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands; [15] Department of Blood and Marrow Transplant, Royal Manchester Children's Hospital, Oxford Road, Manchester

Sponsoring: *The meeting was sponsored by an unrestricted grant from Genzyme Corp., Boston, USA. The sponsor had no influence on the design and execution of the consensus process and meeting, nor on the conclusion.*

Addendum 4

Overview of relevant articles regarding the treatment of MPS I with laronidase.

2.3.a Study a, Kakkis et al. 2001

Study type, start- and enddate:
Phase I/II clinical study. Start- and enddate: not reported.

Intervention:
Patients were given recombinant human alfa-L-iduronidase as a weekly infusion in a dose of 100 units per kg per week during 52 weeks.

Study population:
10 patients with MPS I; 1 Hurler, 8 Hurler-Scheie, 1 Scheie; mean age 12.3 years.

Inclusion criteria:
Patients with MPS I. Diagnosis confirmed by the biochemical determination of alfa-l-iduronidase deficiency in leukocytes.

Exclusion criteria:
Not applicable.

Primary endpoints:
Reduction of spleen and/or liver volume and the reduction of urinary GAG levels.

Secondary endpoints:
Improvements in joint disease, height and weight, sleep apnoea and airway function, cardiac function, visual acuity and functional ability.

2.3.b Study b, Wraith et al. 2004

Study type, start- and enddate:
A randomized, double-blinded, multinational study (phase III clinical trial). Start- and enddate: not reported.

Intervention:
Patients were administered 100 U/kg laronidase, or placebo weekly for 26 weeks.

Study population:
45 patients with MPS I; 1 Hurler, 37 Hurler-Scheie, 7 Scheie; mean age 15.5 years.

Inclusion criteria:
Patients with MPS I, > 5 years of age. Diagnosis confirmed by measurable clinical disease and fibroblast or leukocyte alfa-l-iduronidase activity < 10%.

Exclusion criteria:
Prior tracheostomy or bone marrow transplantation, pregnancy or lactation, administration of any investigational drug within 30 days before study enrollment, medical condition or other circumstance that could significantly interfere with study compliance or known hypersensitivity to laronidase or components of the laronidase or placebo solutions.

Primary endpoints:
Between-group differences in the median change from baseline to week 26 in percent of predicted normal forced vital capacity (FVC) and distance covered in the 6-minute walk test (MWT).

Secondary endpoints:
Liver volume, urinary GAG excretion, sleep study apnoea/hypopnoea index (AHI), active shoulder flexion and the Disability Score Index of the Childhood Health Assessment Questionnaire for patients ≤ 18 years of age and of the Health Assessment Questionnaire for older patients.

2.3.c Study c, Sifuentes et al. 2007

Study type, start- and enddate:

A 6-year single-centre, observational follow-up study. Start- and enddate: not reported.

Intervention:

Patients received weekly laronidase, 100 IU/kg, for a total duration of 6 years.

Study population:

5 of the original 10 patients in the Phase I/II trial; 4 Hurler-Scheie, 1 Scheie; mean age 12.0 years.

Inclusion criteria:

Patients with MPS I. Diagnosis confirmed by biochemical determination of alfa-l-iduronidase deficiency in leukocytes. Those patients who had demonstrated satisfactory infusion-compliance during the initial Phase I/II study were included.

Exclusion criteria:

Not applicable.

Primary endpoints:

Decreased organomegaly, decreased urinary GAG excretion.

Secondary endpoints:

Included the evaluation of multiple clinical manifestations of MPS I in this population.

2.3.d Study d, Wraith et al. 2007

Study type, start- and enddate:
A 52-week, prospective, open-label, multi-centre, multi-national, 'under five' study.
Start- and enddate: not reported.

Intervention:
All patients initially received weekly intravenous infusions of 100 U/kg laronidase. 4 patients with an elevated urinary GAG level noted at 22 weeks qualified to receive a higher dosage (200 U/kg) for the second half of the study.

Study population:
20 patients with MPS I; 16 Hurler, 4 Hurler-Scheie; mean age 2.9 years.

Inclusion criteria:
Patients with MPS I < 5 years old. Diagnosis confirmed by the biochemical determination of alfa-l-iduronidase enzyme activity < 10% of normal in leukocytes or fibroblasts and by genotyping.

Exclusion criteria:
Having undergone or being under consideration for HSCT, acute hydrocephalus, clinically significant organic disease not related to MPS I, administration of an investigational drug within 30 days before study enrollment, or known hypersensitivity to components of the laronidase solution.

Primary endpoints:
Urinary GAG levels, liver edge below the right costal margin, left ventricular mass z score.

Secondary endpoints:
Apnoea/hypopnoea index (AHI).

2.3.e Study e, Clarke et al. 2009

Study type, start- and enddate:
Phase 3 open-label extension trial. Start date: May 2001; end date: March 2005.

Intervention:
Patients were treated with laronidase, 100 IU/kg/week.

Study population:
All 45 patients who participated in the 26-week RCT entered this extension trial. 22 initially received laronidase, 23 initially received placebo. All patients were considered to have attenuated MPS I (38 Hurler-Scheie, 7 Scheie). Mean age at enrollment: 15.7 years. 40 patients completed the trial.

Inclusion criteria:
Patients with MPS I, ≥ 5 years of age. Diagnosis confirmed by measurable clinical disease and fibroblast or leukocyte alfa-l-iduronidase activity ≤ 10%. FVC ≤ 80% of normal. Ability to walk at least 5 m in 6 minutes. The extension trial was open to patients who successfully completed the 26-week RCT.

Exclusion criteria:
Not applicable.

Primary endpoints:
Between-group differences in the median change from baseline to last study visit in percent of predicted normal FVC and distance covered in the 6-MWT.

Secondary endpoints:
Liver volume, urinary GAG excretion, sleep study apnoea/hypopnoea index (AHI), active shoulder flexion, the Disability Score Index of the Childhood Health Assessment, visual acuity, cardiac function, growth.

2.3.f Study f, Giugliani et al. 2009

Study type, start- and enddate:
A randomized, open-label, multicentre, international, dose-optimization trial. Start- and enddate: not reported.

Intervention:
Four treatment regimens studied were: 100 IU/kg weekly, 200 IU/kg every 2 weeks, 200 IU/kg weekly, and 300 IU/kg every two weeks during 26 weeks.

Study population:
The treatment population consisted of 33 patients. 32 patients completed the trial. Group 1 (100 IU/kg weekly): 8 patients; 2 Hurler, 4 Hurler-Scheie, 2 Scheie; mean age at enrollment 8.5 years. Group 2 (200 IU/kg every 2 weeks): 8 patients; 2 Hurler, 5 Hurler-Scheie, 1 Scheie; mean age at enrollment 9.1 years. Group 3 (200 IU/kg weekly): 8 patients; 3 Hurler, 2 Hurler-Scheie, 3 Scheie; mean age at enrollment 8.6 years. Group 4 (300 IU/kg weekly): 9 patients; 3 Hurler, 5 Hurler-Scheie, 1 Scheie; mean age at enrollment 9.3 years.

Inclusion criteria:
Patients had to weigh ≥ 12.5 kg, have clinical symptoms of MPS I, have < 10% of normal alfa-l-iduronidase enzyme activity in leukocytes or fibroblasts, and have normal renal function as indicated by serum creatinine and blood urea nitrogen levels.

Exclusion criteria:
Patients were excluded if they had previously received treatment with laronidase, HSCT or other major organ transplantation; had a known hypersensitivity to components of laronidase infusion; had other significant medical problems; had received other investigational drug within 30 days of enrollment.

Primary endpoints:
Difference in percentage change from baseline to final visit in mean urinary GAG levels.

Secondary endpoints:
Differences between groups in the mean percentage change in liver organ volume and the mean absolute change in the 6-MWT distance in meters for ambulatory patients > 5 years old.

2.3.g Study g, Cox-Brinkman et al. 2007

Study type, start- and enddate:

Single-institutional, prospective cohort trial. Start- and enddate: not reported.

Intervention:

Patients were treated with laronidase, 100 IU/kg/week, during 12 months.

Study population:

Six patients with attenuated MPS I (Scheie phenotype) were included. Mean age at baseline 6.3 years.

Inclusion criteria:

Patients with attenuated MPS I.

Exclusion criteria:

Not applicable.

Primary endpoints:

Range of motion.

Secondary endpoints:

Functional status.

2.3.h Study h, Arora et al. 2007

Study type, start- and enddate:

Single-institutional, retrospective cohort trial. Start- and enddate: not reported.

Intervention:

Patients received ERT, 100 IU/kg/week. Median duration of follow-up was 22.5 months.

Study population:

14 MPS I Hurler-Scheie patients homozygous for the p.Leu490Pro missense mutation. All patients were of Pakistani/Kashmiri descent. One patient died before start ERT, one patient was transplanted. 12 patients received ERT. Median age at baseline 8.6 years.

Inclusion criteria:

MPS I patients homozygous for the p.Leu490Pro missense mutation.

Exclusion criteria:

Stem cell transplantation.

Primary endpoints:

Urinary GAG levels

Hepatosplenomegaly

Growth.

Secondary endpoints:

Not applicable.

2.3.i Study i, Gabrielli et al. 2009

Study type, start- and enddate:
Case report. Start- and enddate: not reported.

Intervention:
Patients were treated with weakly intravenous laronidase, 100 IU/kg and compared after 5 years of treatment.

Study population:
A boy with attenuated MPS I who had laronidase initiated at the age of 5 months. His clinical course was compared to that of his older sister, who began treatment at 5 years of age.

Inclusion criteria:
Not applicable.

Exclusion criteria:
Not applicable.

Primary endpoints:
Urinary GAG levels
Hepatosplenomegaly
Cardiac function
Joint mobility
Eye disease
Hearing impairment
Skeletal disease
Growth
Development.

Secondary endpoints:
Not applicable.

2.3.j Study j, Tylki et al. 2010

Study type, start- and enddate:
Single-institutional, retrospective and prospective cohort trial. Start- and enddate: not reported.

Intervention:
Patients were followed from birth until the introduction of ERT. Patients received intravenous laronidase, 100 IU/kg/week, for 52-260 weeks.

Study population:
14 patients with MPS I; 10 Hurler, 1 Hurler-Scheie, 3 Scheie; mean age 4.8 years at start of treatment. Group 1: consisted of 7 patients who were 1 year old at the time of introduction of ERT. Group 2: consisted of 7 patients who were at least 3 years of age at the time of introduction of ERT.

Inclusion criteria:
MPSI, diagnosis confirmed by biochemical determination of alfa-l-iduronidase enzyme activity in leukocytes and by molecular analysis. Naive to laronidase therapy.

Exclusion criteria:
Not applicable.

Primary endpoints:
Height
Weight
Head circumference
Chest circumference.

Secondary endpoints:
Urinary GAG levels.

2.3.k Study k, Tylki et al. 2010

Study type, start- and enddate:
Single-institutional, prospective cohort trial. Start- and enddate: not reported.

Intervention:
Patients were followed from the first year of life until the introduction of ERT and after 52-208 weeks of treatment with laronidase, 100 IU/kg/week.

Study population:
17 patients with MPS I. Median age at baseline 8.6 years.
Group 1: 10 patients with MPS I, Hurler phenotype.
Group 2: 7 patients with MPS I; 2 Hurler-Scheie, 5 Scheie.

Inclusion criteria:
MPSI, diagnosis confirmed by biochemical determination of alfa-l-iduronidase enzyme activity in leukocytes and by molecular analysis. Naive to laronidase therapy.

Exclusion criteria:
Not applicable.

Primary endpoints:
Range of motion
Functional status.

Secondary endpoints:
Not applicable.

2.3.l Study l, Grewal et al. 2005

Study type, start- and enddate:

Multi-institutional, retrospective case series. Start- and enddate: not reported.

Intervention:

Patients were treated with laronidase prior to HSCT, 100 IU/kg/week.

Study population:

12 MPS I Hurler patients; median age at initiation of ERT 12 months.

Inclusion criteria:

Patients with MPS I Hurler syndrome (diagnosis established by clinical features and deficient activity of leukocyte α-L-iduronidase) who had ERT and HSCT combination therapy.

Exclusion criteria:

Not applicable.

Primary endpoints:

Pulmonary complications associated with HSCT.

Secondary endpoints:

Donor engraftment
Urinary GAG levels.

2.3.m Study m, Cox-Brinkman et al. 2006

Study type, start- and enddate:
Multi-institutional, retrospective cohort study. Start- and enddate: November 2003 – April 2005.

Intervention:
ERT was given weekly in a dosage of 100 IU/kg prior to HSCT.

Study population:
22 MPS I Hurler patients. Median age at HSCT: 18 months.

Inclusion criteria:
MPS I Hurler patients who were considered eligible for HSCT. Diagnosis confirmed on the basis of deficiency of leukocyte α-L-iduronidase in combination with the clinical phenotype.

Exclusion criteria:
Not applicable.

Primary endpoints:
The 'alive and engrafted rate'.

Secondary endpoints:
HSCT-associated morbidity.

2.3.n Study n, Tolar et al. 2008

Study type, start- and enddate:

Single-institutional, prospective trial. Start- and enddate: between 2004 and 2007.

Intervention:

ERT was administered weekly at a dose of 100 IU/kg prior to HSCT.

Study population:

Seven MPS I Hurler patients. Median age at HSCT: 18 months.

Inclusion criteria:

Patients with MPS I Hurler, eligible for HSCT. Diagnosis based on clinical phenotype, mutation analysis of IDUA gene and enzyme activity.

Exclusion criteria:

Not applicable.

Primary endpoints:

Engraftment
Pulmonary complications associated with HSCT.

Secondary endpoints:

Overall morbidity.

2.3.o Study o, Wynn et al. 2009

Study type, start- and enddate:

Single-institutional, prospective cohort study. Start- and enddate: February 2004 – January 2008.

Intervention:

All patients received ERT in a dosage of 100 IU/kg/week before HSCT.

Study population:

18 MPS I Hurler patients. Mean age at HSCT: 12 months.

Inclusion criteria:

MPS I Hurler patients eligible for HSCT. Diagnosis was based on deficient enzyme activity and mutation analysis.

Exclusion criteria:

Not applicable.

Primary endpoints:

Overall survival
Engraftment rate.

Secondary endpoints:

HSCT-associated morbidity.

Addendum 5

Important issues needing further study ('witte vlekken analyse')

1. In order to further substantiate the efficacy of laronidase on relevant outcome parameters, additional long-term outcome are needed. Ideally, subgroups of MPS I patients should be analyzed to take into consideration the different MPS I phenotypes (Hurler/Hurler-Scheie/Scheie) and the different stages (i.e. different burden) of disease.
2. To date, due to its rarity, there is paucity of data on the natural history of MPS I Hurler-Scheie patients. Long-term follow-up data on patients with this phenotype, especially regarding central nervous system involvement, are necessary to gain more insight in the optimal therapy for patients in this phenotypcial subgroup: HSCT or ERT.
3. There is a need for a reliable biomarker in MPS I in order to monitor treatment efficacy, as the course of the disease in generally slow and patients treated with laronidase differ substantially in severity and stage of the disease, complicating reliable assessment of therapeutic efficacy on clinical endpoints.
4. Since early initiation of treatment in MPS I patients may significantly delay the onset of major clinical signs and symptoms of the disease, early diagnosis through newborn screening for MPS I would provide a critical therapeutic window.
5. Although a dose-optimization trial of laronidase (Giugliani et al., 2009) showed that the approved laronidase dose regimen (100 IU/kg/week) had similar efficacy and potentially improved safety compared to other dose regimens, long-term effects of alternative dosing regimes (e.g. 200 IU/kg every 2 weeks) are unknown.
6. Most MPS I patients on chronic treatment with laronidase show a rapid increase in antibodies against the drug. It is not yet clear how antibodies may affect the efficacy of recombinant proteins that are prescribed to treat lysosomal storage disorders, including laronidase in MPS I. Dickson et al. (2008) demonstrated that antibodies against recombinant human α-L-iduronidase can reduce the efficacy of ERT for MPS I in dogs. Moreover, this study showed that a transient immunosuppressive regimen can prevent antibody formation, resulting in improved enzyme uptake in organs. Whether transient immunosuppression may enhance ERT for human MPS I patients remains to be elucidated.

Current relevant studies on these issues (point-by-point)

1. International data on MPS I patients, with or without treatment, are captured in the MPS I Registry, an observational database (Genzyme sponsored). However, the observational and non-committing character of this Registry may prevent analysis of good quality longitudinal data. A prospective international cohort study may be the best strategy. However, funding for such a long-term study is difficult to ascertain.
2. There is a European initiative to try to capture relevant natural history data on patients with the intermediate phenotype (Hurler-Scheie phenotype) from several of the larger clinics in Europe. This study is in the preliminary phase.
3. In 2010 a patient-reported outcome study on patients with mucopolysaccharidosis was started by Erasmus MC and the VKS, with the support of other centers including UMCU and AMC. The aims of this study are to include the patients' point of view in the characterization and description of the mucopolysaccharidoses, to compare the different types of mucopolysaccharidoses, and to evaluate the long-term effects of available treatment options and support measures on selected patient-reported outcome measures.
4. Several potential biomarkers (e.g. heparin cofactor II – Thrombin complex) are currently under study. Again, the rarity of the disease and its broad phenotypic spectrum complicate these studies. Additional complicating factors are the fact that almost all MPS I patients in the 'western world' are already treated with laronidase for a longer period and the lack of large scale bio-banks containing plasma and urine samples before and during treatment. For future studies, international collaboration and the start of such bio-banks are essential.
5. Several studies on the feasibility of newborn screening for MPS I, both from a technical as well as from an ethical and point of view are currently conducted, also within the Netherlands (TI-Pharma initiative, including UMCU, ErasmusMC and AMC).
6. As far as we know, there are no dose optimization studies being done. Again, such studies are complicated by the broad phenotypic spectrum of the disease and the lack of good biomarkers for disease severity, disease progression and therapeutic efficacy.
7. Currently, there is one ongoing study with the purpose to determine whether the development of antibodies to laronidase in patients with MPS I receiving laronidase impairs the clearance of GAG substrate. Another ongoing study was designed to see if the treatment with an antigen-specific immunosuppressive can decrease or stop an antibody response to laronidase during enzyme replacement therapy in severe MPS I patients. Both studies are sponsored by Genzyme, participants are being recruited (www.clinicaltrials.gov).

Addendum 6

Relevant biographies of participants in this review (on request by ZonMw)

Relevant competing interests related to the disease, the drug under review (Laronidase) and the company producing the drug (Genzyme Corp.).

- Prof.dr. Frits A. Wijburg
    - Chairs the division of pediatric metabolic diseases of the AMC in Amsterdam and is a board member of the Amsterdam Lysosome Center Sphinx. The AMC is one of the two centers in the Netherlands where Laronidase is prescribed.
    - Chair of the European Board of the MPS I Registry (this is an international observational database on patients with MPS I, sponsored by Genzyme).
    - Received reimbursements for travel for various meetings on lysosomal storage disorders, including MPS I, from Genzyme.
    - Received speakers fees for presentations on MPS I from Genzyme.
    - Has acted as temporary consultant for Genzyme on various lysosomal storage diseases, including MPS I.
    - Has received research funding from Genzyme for studies on mucopolysaccharidosis, including MPS I.

- Prof.dr. Ans van der Ploeg
    - Chairman Center for Lysosomal en Metabolic Diseases at Erasmus MC University Medical Center and chair of the division of pediatric metabolic diseases and genetics at Erasmus MC University Medical Center, Sophia Children's Hospital.
    - Principal investigator of the "MPS I Under Five Sudy". This was a sponsor driven study by Genzyme Corp. The results of the study were published in: Wraith J.E., Beck M, Lane R, Van der Ploeg A.T., Shapiro E., Guffon N. **2007.** Enzyme reaplacement therapy for mucopolysaccharidosis I patients less than 5 years old: Results of a multinational study of recombinant human α-L-iduronidase (Laronidase). Pediatrics, 120: e37-46.
    - As of August 2004, ATvdP provides consulting services for Genzyme Corp, Cambridge, MA, USA, under an agreement between Genzyme Corp and Erasmus MC, Rotterdam, the Netherlands. This agreement also caters to financial support for Erasmus MC for research in Pompe's disease. Erasmus MC and inventors for the method of treatment of Pompe's disease by enzyme replacement therapy receive royalty payments pursuant to Erasmus MC policy on inventions, patents and technology transfer.

- Dr. T.J. de Koning
    - Head department of Metabolic Diseases University Medical Centre Utrecht, actively involved in HSCT for Hurler disease.
    - Chair clinical study group metabolic diseases and endocrinology, Medicines for Children's Research Network (MCRN).
    - No conflicting interests regarding the drug or companies.

- J.C. Brugma MSc. PharmD
    - Pharmacist of the hospital pharmacy Erasmus MC, Rotterdam and member of the Centre for Lysosomal and Metabolic Diseases, Erasmus MC Rotterdam.
    - PhD student Erasmus MC, Rotterdam and institute for Medical Technology Assessments, in this position question the efficacy and efficiency investigation of Myozyme.
    - Received reimbursement for travel for a meeting on lysosomal storage disorders, mostly about Pompe disease, from Genzyme.

- H.K. Meutgeert-Dekker
    - Is working as executive director of VKS, the Dutch patient organization for adults and children with metabolic diseases. MPS I is one of the 160 specific diseases VKS represents.
    - Member of the Dutch steering committee on Orphan Medicinal Products.
    - Participant in the EU patient advisory board sponsored by Genzyme (this group addresses patient advocacy issues in all European countries).
    - Received reimbursement of travel costs and conference fees for various meetings on lysosomal storage diseases including MPS I, from Genzyme.
    - Has received funding from Genzyme for the production of short audiovisual portraits of MPS patients.
    - VKS receives sponsoring of activities we organize for our members from a total of four pharmaceutical companies. Genzyme is one of them.

- Dr. M.Hagemans
    - Senior researcher at the Erasmus MC Center for Lysosomal and Metabolic Diseases. The Erasmus MC is one of the two centers in the Netherlands where Laronidase is prescribed.
    - Received reimbursements for travel for various meetings on lysosomal storage disorders, including MPS I, from Genzyme.
    - Received speaker's fees for presentations on Pompe disease (another lysosomal storage disorder) under an agreement between Genzyme Corp. and Erasmus MC, Rotterdam.
    - Has received research funding for studies on Pompe disease under an agreement between Genzyme Corp. and Erasmus MC, Rotterdam.

- Drs. M.H. de Ru
    - Paediatrician and fellow for metabolic diseases at the AMC in Amsterdam.
    - Involved in the treatment of MPS I patients on Aldurazyme.
    - PhD student on MPS I in the AMC in Amsterdam.
    - No conflicts of interest to report (received no funding from Genzyme).