

Efficacy of Enzyme Replacement Therapy on the range of motion of the upper and lower extremities in 16 Polish patients with mucopolysaccharidosis type II: A long-term follow-up study

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Background: Enzyme replacement therapy (ERT) with idursulfase is available for patients with mucopolysaccharidosis (MPS) type II, and improvements in certain somatic signs and symptoms have been reported. The aim of the study was to assess the effectiveness of ERT with idursulfase (Elaprase®) on the passive joint range of motion (JROM) in the upper and lower extremities of patients with MPS II. **Methods:** The study included 16 Polish patients diagnosed with MPS II and followed in our Institute in the years 2009–2016. The study group was divided for groups of neuronopathic (group 1, n=12) and non-neuronopathic (group 2, n=4) patients. A passive JROM was measured with a goniometer by one physiotherapist, while in group 1 it was assessed at baseline and after both short-term (52 weeks) and long-term (mean 230 weeks, range: 108–332 weeks) ERT. In group 2, it was assessed at baseline and after short-term ERT (68–85 weeks, no data for long-term ERT). **Results:** In group 1, after 52 weeks of ERT, we observed some improvement of passive ROM in wrist flexion (5/12 patients), shoulder abduction and wrist extension (3/12 patients), shoulder flexion, elbow and knee extension (2/12 patients). After long-term ERT (mean 230 weeks), the improvement in JROM was observed only in 2 patients. There was no improvement in the shoulder abduction, elbow flexion and extension, hip and knee extension. In group 2, the improvement in passive ROM was observed in several joints: shoulder flexion, wrist flexion and extension improved (2/4 patients) and shoulder abduction (1/4 patients). **Conclusion:** ERT is of low efficacy on correcting the range of motion of joints in MPS II patients.

Keywords: mucopolysaccharidosis type II; enzyme replacement therapy; range of motion; bone and joint disease

Received: 08 December, 2021; **revised:** 07 January, 2022; **accepted:** 07 January, 2022; **available on-line:** 28 February, 2022

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Abbreviations: ERT, enzyme replacement therapy; I2S, iduronate-2-sulfatase; JROM, joint range of motion; MPS, mucopolysaccharidosis

INTRODUCTION

Mucopolysaccharidosis (MPS) type II, also known as Hunter syndrome (# 309900), is an X-linked lysosomal storage disease characterized by a multi-systemic involvement and progressive clinical course (Tyłki-Szymańska *et al.*, 2014; Scarpa *et al.*, 2011). MPS II is caused by hemizygous pathogenic variants of the *IDS* gene resulting in the deficient activity of the enzyme, iduronate-2-sulfatase (I2S, EC 3.1.6.13), and characterized by the accumulation of glycosaminoglycans (GAGs) (Tyłki-

Szymańska *et al.*, 2014; Scarpa *et al.*, 2011). The impactful difference in disease progression and clinical outcome is attributable to the presence or absence of primary neuronopathic disease (Beck *et al.*, 2010; Shapiro *et al.*, 2016). A degenerative joint and bone disease is due to the lack of skeletal remodelling, disordered endochondral and intramembranous ossification, disruption of normal elastogenesis, and the deposition of GAGs in muscles, tendons, and ligaments (Hinek *et al.*, 2000; Simonaro *et al.*, 2008). The severity of motor compromise is caused by deposition of GAGs in the soft tissue of core and periphery structures (cervical compression, hydrocephalus, carpal tunnel syndrome), and often determines other functional abilities.

In 2006, Enzyme Replacement Therapy (ERT) with recombinant human I2S (Elaprase®, Shire Human Genetic Therapies, Inc., Cambridge, MA, USA) was approved for the treatment of Hunter syndrome addressing the underlying pathophysiology by delivering sufficient I2S to reverse and prevent GAG accumulation (Muenzer *et al.*, 2006; Muenzer *et al.*, 2007; Muenzer *et al.*, 2011).

The aim of the study was to assess the effectiveness of ERT with idursulfase (Elaprase®) on the passive joint range of motion (JROM) in the upper and lower extremities of patients with MPS II diagnosed and treated in one centre in the years 2009–2016.

PATIENTS AND METHODS

Patients

The study included 16 Polish patients (15 male and one female) diagnosed with MPS II and followed in one centre (Children's Memorial Health Institute, CMHI, Warsaw, Poland) during the years 2009–2016. All the study patients received ERT with recombinant human I2S (Elaprase®), 0.5 mg/kg weekly intravenously. Individual patient's characteristics is presented in Table 1.

Methods

The diagnosis of MPS II was confirmed by the demonstration of reduced iduronate-2-sulfatase activity in the serum or peripheral blood leukocytes. Sequence analysis of the *IDS* gene was performed by targeted gene sequencing.

The study group was divided for groups of neuronopathic (group 1, n=12) and non-neuronopathic (group 2, n=4) patients, see Table 1. The passive joint range of motion (JROM) was measured in degrees with a goniometer and was assessed by one physiotherapist (JM) using the International Method of Measuring and Re-

Table 1. Study patients' characteristics.

Patient No	Age at diagnosis	Age at the start of ERT	Duration of treatment (weeks) short-/long-term ERT	Molecular analysis	MPS phenotype	Family background
Group 1						
01	1 mo	3 mo	52/332	c.1568A>G, p.Tyr523Cys	Neuronopathic (severe)	Sibling
02*	5 y	10 y	52/208	c.1568A>G, p.Tyr523Cys/ c.1568A>G, p.Tyr523Cys	Neuronopathic (severe)	Sibling
03	1.5 y	3 y	52/234	c.908_909del, p.Ser303fs	Neuronopathic (severe)	maternal first cousin
04	2 y	3 y	52/208	c.908_909del, p.Ser303fs	Neuronopathic (severe)	maternal first cousin
05	1 y 3 mo	3 y	52/312	c.998C>T, p.Ser333Leu	Neuronopathic (severe)	None
06	3 y 4 mo	4 y	52/208	c.998C>T, p.Ser333Leu	Neuronopathic (severe)	None
07	3 y	3 y	52/260	c.998C>T, p.Ser333Leu	Neuronopathic (severe)	None
08	2 y 10 mo	3 y	52/216	c.1007G>A, p.Gly336Val	Neuronopathic (severe)	None
09	2 y 3 mo	3 y	52/208	n.a.	Neuronopathic (severe)	None
10	3.5 y	4 y 4 mo	52/260	c.1239_1240insCT, p.Ala414fs	Neuronopathic (severe)	None
11	4 y	11 y 8 mo	52/208	c.879G>A, p.Gln293Gln	Neuronopathic (severe)	None
12	3.5 y	11 y 8 mo	52/108	c.1478G>C, p.Arg493Pro	Neuronopathic (severe)	None
Group 2						
13	8.5 y	12.5 y	82	c.181T>C, p.Cys61Gly	Non-Neuronopathic	None
14	6.5 y	12 y 9 mo	85	c.1030G>A, p.E344*	Non-Neuronopathic	None
15	1 y 3 mo	26 y	68	c.1034G>T, p.Trp345Ser	Non-Neuronopathic	maternal first cousin
16	5 y	28 y	68	c.1034G>T, p.Trp345Ser	Non-Neuronopathic	maternal first cousin

Abbreviations: y, years; mo, months; n.a., not analyzed; *female.

cording Joint Motion (SFTR; sagittal, frontal, transverse, rotation) (Gerhardt *et al.*, 2001; Marucha *et al.*, 2012). In patients from group 1, passive JROM was assessed at baseline and over the course of short-term (52 weeks) and long-term (mean 230 weeks, range: 108–332 weeks) ERT. In patients from group 2, passive JROM was assessed at baseline and over the course of short-term ERT (68–85 weeks, no data for long-term ERT).

The Sign test and *p*-value were used to assess the efficacy of ERT with idursulfase on the passive JROM. Ethical approval was obtained from the Children's Memorial Health Institute Bioethical Committee, Warsaw, Poland.

RESULTS

Study's population

The mean patient age at MPS II diagnosis was 3 years and 4 months (age range: 1 month – 8.5 years). One patient (Patient 01) was diagnosed through family

screening (his older sister – Patient 02 – had a diagnosis of MPS II). Twelve out of 16 (75%) patients presented with a neuronopathic (severe) phenotype, while 4 others showed the attenuated phenotype.

The mean age at ERT initiation was 8 years and 8 months (age range: 3 months – 28 years).

Range of motion

Group 1 – neuronopathic (severe) phenotype, n=12

After the short-term ERT, a passive ROM of the wrist flexion improved in 5 (42%) patients, while of shoulder abduction and wrist extension improved in 3 (25%) patients, and of shoulder flexion as well as elbow and knee extension improved in 1 (8%) patient (Table 2 and Fig. 1). In four (33%) patients there was observed an improvement in passive ROM of at least two joints. There was no improvement in the hip extension.

After long-term ERT, there was observed an improvement of a passive ROM in two (16%) patients.

Table 2. Efficacy of short-term and long-term ERT on passive JROM of the upper and lower extremities in group 1. JROM values (in degrees) for each patient were presented in one row as following: at baseline, after short-term ERT, after long-term ERT. An increase in passive ROM of at least 10° was considered an improvement and indicated by bold font.

Movement in degrees Passive ROM (normal)	Shoulder flexion (°)	Shoulder abduction (°)	Elbow flexion (°)	Elbow extension (°)	Wrist flexion (°)	Wrist extension (°)	Hip extension (°)	Knee extension (°)
	180	180	155	0	90	80	20	0
Patient no								
01	180/170/140	180/160/130	155/155/155	0/0/0	90/90/80	80/80/60	20/20/20	0/0/0
02	120/120/120	100/90/90	150/140/150	-40/-30/-45	40/50/30	20/20/10	0/0/-20	-10/0/-20
03	170/160/130	160/150/80	150/150/140	0/-5/-30	80/40/40	60/20/10	20/0/20	-10/0/0
04	150/140/130	150/130/90	150/150/130	-10/-20/-45	70/50/60	60/50/40	20/20/-40	-5/-10/-30
05	150/170/110	130/150/90	150/150/100	-10/0/-30	80/90/40	70/80/10	20/0/-20	-5/-20/-20
06	150/140/130	140/140/100	120/150/130	0/0/-30	90/90/70	80/80/20	0/0/-20	-10/-10/-30
07	170/170/160	170/170/140	155/155/125	0/0/-30	90/90/90	80/80/30	0/0/0	-20/-20/-30
08	150/130/130	130/120/110	155/150/130	-20/-20/-20	90/90/90	80/70/30	20/20/0	0/0/-10
09	140/140/130	130/140/110	150/150/130	-10/-20/-30	80/90/80	70/80/40	20/20/0	0/0/-10
10	140/150/120	140/150/110	150/150/130	-20/-20/-30	70/80/80	50/60/40	20/0/0	-20/-20/-15
11	130/120/140	130/110/120	150/120/130	-40/-50/-40	40/20/50	20/10/30	0/0/0	0/0/-20
12	120/110/110	120/90/90	150/120/120	-40/-50/-50	30/60/10	20/0/0	0/0/-30	-10/-20/-30
Mean	147.5/143.3/129.2	140.0/134.2/105.0	148.8/145.0/130.8	-15.8/-17.9/-31.7	70.8/70.0/60.0	57.5/52.5/26.7	11.7/6.7/-7.5	-7.5/-8.3/-17.9
S.D.	19.1/21.0/13.8	22.2/25.4/18.3	9.3/12.2/14.0	16.2/18.3/13.2	21.9/24.9/25.9	24.5/31.4/17.2	10.3/9.8/18.6	7.2/9.4/11.2
*Sign test	1.845	0.948	0.894	1.061	0.667	0.667	0.154	0.405
*p-value	0.235 (ns)	0.342 (ns)	0.371 (ns)	0.289 (ns)	0.505 (ns)	0.505 (ns)	0.24 (ns)	0.686 (ns)
**Sign test	2.214	3.015	2.667	2.667	1.581	1.809	1.768	2.267
**p-value	0.027 (s)	0.003 (s)	0.008 (s)	0.008 (s)	0.114 (ns)	0.070 (ns)	0.077 (ns)	0.023 (s)

Abbreviations: (s) statistically significant, (ns) statistically non-significant, *comparison between baseline and JROM after short-term ERT, **comparison between baseline and JROM after long-term ERT.

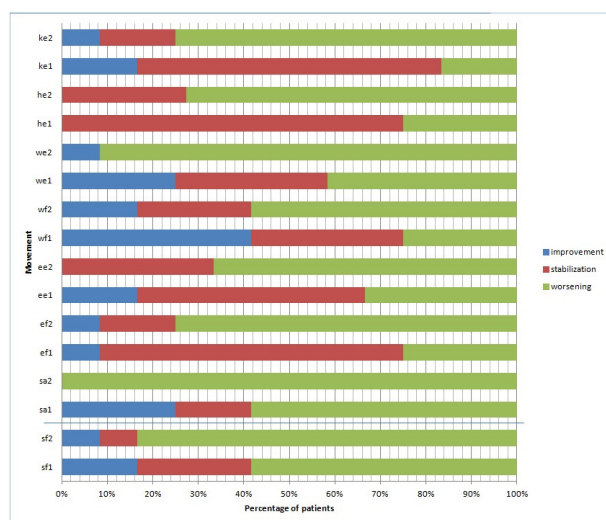


Figure 1. Efficacy of short- and long-term ERT on passive JROM of the upper and lower extremities in group 1. Abbreviations: 1, short-term ERT; 2, long-term ERT; sf, shoulder flexion; sa, shoulder abduction; ef, elbow flexion; ee, elbow extension; wf, wrist flexion; we, wrist extension; he, hip extension; ke, knee extension.

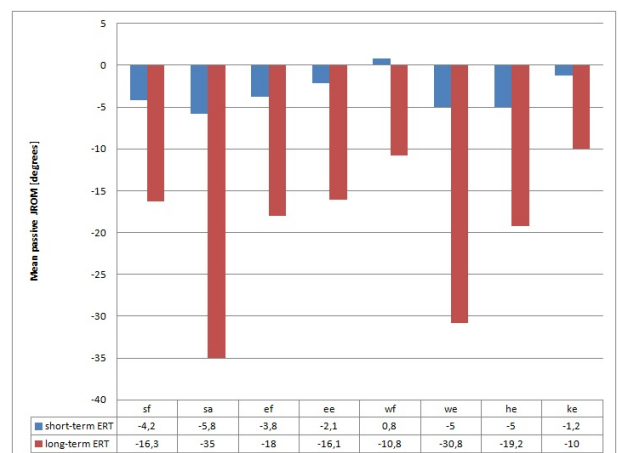


Figure 2. Mean passive JROM (degrees) for all patients from group 1 at baseline and after short-term (52 weeks) and long-term (mean 230 weeks) ERT. Abbreviations: sf, shoulder flexion; sa, shoulder abduction; ef, elbow flexion; ee, elbow extension; wf, wrist flexion; we, wrist extension; he, hip extension; ke, knee extension.

Table 3. Efficacy of short-term ERT on passive JROM of the upper and lower extremities in group 2.

JROM values (in degrees) for each patient were presented in one row as following: at baseline, after short-term ERT. An increase in passive ROM of at least 10° was considered an improvement and indicated by bold font.

Movement in degrees Passive ROM (normal)	Shoulder flexion (°)	Shoulder abduction (°)	Elbow flexion (°)	Elbow extension (°)	Wrist flexion (°)	Wrist extension (°)	Hip extension (°)	Knee extension (°)
	180	180	155	0	90	80	20	0
Patient no								
13	130/ 140	110/110	150/140	-30/-40	40/ 50	10/ 20	20/20	0/0
14	130/120	130/120	150/150	-35/-45	25/ 45	20/ 30	20/20	0/0
15	90/90	60/ 70	150/120	-40/-50	20/20	0/0	0/-20	-20/-30
16	110/ 120	100/100	150/150	-40/-40	80/70	20/20	20/0	0/0
Mean	115.0/117.5	100/100	150/140	-36.3/43.8	41.3/46.3	12.5/17.5	15.0/15.0	-5.0/-7.5
S.D.	19.1/20.6	29.4/21.6	0.0/14.1	4.8/4.8	27.2/20.6	9.6/12.6	10.0/10.0	10.0/15.0
Sign test	0.534	-0.707	1.342	1.155	0.534	1.342	-	-
p-value	0.593 (ns)	0.479 (ns)	0.179 (ns)	0.248 (ns)	0.593 (ns)	0.179 (ns)	-	-

Abbreviations: (s) statistically significant, (ns) statistically non-significant.

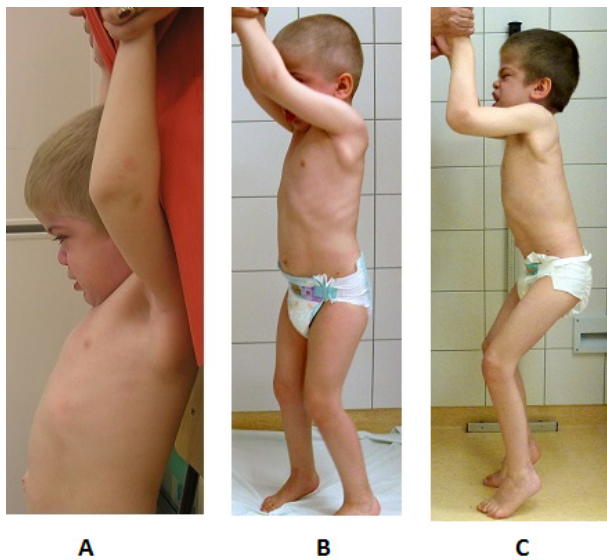


Figure 3. Clinical pictures of Patient 07 with neuronopathic (severe) phenotype at baseline (A), after 52 weeks of ERT (B), after 7 years of ERT (C).

The wrist flexion improved in 2 (16% *vs.* 42% after short-term ERT) patient while shoulder flexion and elbow extension in 1 (8% *vs.* 8% after short-term ERT) patient (Table 2 and Fig. 1). There was no improvement in the shoulder abduction, elbow flexion and extension, hip and knee extension.

The passive JROM improvement between baseline and after both 52 weeks of ERT (short-term ERT) and 230 weeks (mean time of long-term ERT) was not statistically significant (Table 2).

The degree of restriction of passive JROM in the upper and lower extremities after short- and long-term ERT was presented in Fig. 2. A passive ROM of the shoulder abduction (Fig. 3), wrist extension and hip extension were the most restricted movements (-35, -30.8 and -19.2 degrees, respectively, after long-term ERT), while the wrist flexion was the least restricted.

Group 2 (attenuated phenotype, n=4)

In group 2, a passive ROM of the shoulder flexion, wrist flexion and extension improved in 2 (50%) patients, while shoulder abduction in 1 (25%) of those patients (Table 3). There was no improvement in elbow flexion and extension, knee and hip extension.

DISCUSSION

Joint stiffness is a typical feature of MPS II patients, however studies on the mobility profile of MPS patients are scarce. In our previous study we described an early ROM impairment in children with MPS II (Marucha *et al.*, 2012). Restrictions in shoulder joints were the earliest being observed already before the second year of life. Since ERT with idursulfase became available for MPS II patients, many studies reported its clinical efficacy (7–9). It is known that the response to ERT appears to depend on the severity of the condition of individuals and the age at which ERT begins (Tylki-Szymańska *et al.*, 2012). One of our patients (Patient 01) started treatment before the onset of irreversible changes which allowed the slower progression of passive JROM.

There is little information about the clinical efficacy of ERT with idursulfase on the JROM of MPS II patients. Thus, we conducted the study aiming to assess the efficacy of ERT on the passive JROM of the upper and lower extremities in a cohort of 16 Polish MPS II patients, diagnosed and followed in our Institute. Our study presents one of the longest observation periods, reported in the literature, on the efficacy of ERT with idursulfase on the JROM in patients with MPS type II. We have observed no significant improvement in passive JROM of patients with both neuronopathic (severe) and attenuated forms of MPS II treated with ERT. Shoulder abduction, wrist extension and hip extension were the most restricted joint movements.

Our observations are similar to those reported in the literature. Lampe and others described the efficacy of long-term (≥ 2 years continuously) ERT in a series of severe MPS II patients from five international centres (Lampe *et al.*, 2014). An improvement in JROM was reported for 7/21 patients (33%), while 13/21 patients (62%) showed the stabilization of joint disease. Tomanin

and others described the clinical efficacy of long-term (3.5 years) ERT in 27 Hunter patients (17 patients with severe form and 10 with attenuated form starting ERT between 1.6 and 27 years of age) (Tomanin *et al.*, 2014). An improvement in JROM was reported in the upper extremity of 43% of patients starting ERT before 12 years of age and of 41% of patients older than 12 years. In our study, JROM was assessed after a longer period of ERT (mean 230 weeks) and the improvement was observed in a minor percentage of patients (16% *vs.* 33%).

Parini and others reported the outcomes of 17 patients (including 11 with severe phenotype) treated in a single centre, while 16 of them were treated for a minimum of 5 years (Parini *et al.*, 2015). The improvement in JROM was noted over the first two years of ERT for the shoulders, elbows, hips and knees. However, after 5 years of treatment it changed only for the right shoulder compared to baseline.

In the largest 2-year extension study of idursulfase treatment of 94 patients with Hunter syndrome, Muenzer and others observed clinically important improvements in JROM only for combined shoulder flexion/extension and shoulder abduction; no improvement was seen for other joints (Muenzer *et al.*, 2011). Our results are opposite to these observations, ROM of the shoulder abduction is one of the most restricted movements.

CONCLUSIONS

ERT with idursulfase is of low efficacy on correcting the passive range of motion of joints in patients with MPS type II.

Authors' contribution

JM designed the study, collected, and analysed clinical data, interpreted the results, wrote the manuscript. PL critically revised and approved the final manuscript. ATS critically revised and approved the final manuscript.

Conflicts of interest

The authors declare no conflict of interest.

Data Availability Statement

All data generated or analyzed during this study are included in this published article.

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