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Efficacy and Safety of Enzyme Replacement Therapy in Children with Mucopolysaccharidosis Type I, II, and VI: A Single-Center Cohort Study

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Background. *There are limited data on the efficacy of long-term enzyme replacement therapy (ERT) in children with mucopolysaccharidosis (MPS).* ***Objective.*** *Our aim was to study the efficacy and safety of long-term ERT in children with MPS type I, II and VI.* ***Methods.*** *We analyzed the results of ERT with laronidase, idursulfase and galsulfase in children with MPS type I, II and VI admitted to the federal research center from January 2007 to November 2016. The response rate was assessed by the level of normalized urinary excretion of glycosaminoglycans (GAGs) (the ratio of GAGs concentration to urine creatinine) recalculated in percent (%) exceedance of the upper limit of normal for the corresponding age. Data on the administered therapy and its results, including adverse events, is extracted from the medical records of in-patients.* ***Results****. The results of treatment (intravenous infusions, intervals between administrations from 4 to 10 days) were studied in 33 children (5 of them were girls) with MPS type I (n =4; laronidase at a dose of 0.58 mg/kg), II (n =26; idursulfase at a dose of 0.5 mg/kg), and VI (n =3; galsulfase at a dose of 1 mg/kg). A decrease in the normalized urinary excretion of GAGs from 376% (172; 791) to 54% (0; 146) exceedance of the upper limit of normal for the age (p <0.001) was noted in the course of ERT lasting (median) 27 (14; 41) months. A decrease in the normalized GAGs excretion below the upper limit of normal for the age was established in 12/33 (36%) patients. ERT-associated adverse events were identified in 12 patients; one case required a two-fold therapy interruption. The development of nephrotic syndrome in the course of ERT in patients with severe MPS II was first described.* ***Conclusion****. Long-term ERT in children with MPS type I, II and VI is characterized by acceptable efficacy and safety.*
Key words*: children, mucopolysaccharidosis, enzyme replacement therapy, laronidase, idursulfase, galsulfase, glycosaminoglycans.*
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Table 1. Dynamics of urinary GAGs excretion in children with MPS in the course of ERT

Indicators	**Initially*** ***n* = 33**	**On ERT**** ***n* = 33**	***p***
Age at urine sampling, months min−max	57 (30; 95) 6−192	119 (63; 136) 13−208	0.001
Normalized GAGs excretion, %*** min−max	376 (172; 791) 21−1989	54 (0; 146) 0−440	0.001

Note. * — the time point corresponding to the time of the first urine sampling to determine GAGs excretion (in 8 patients, the urine analysis was performed after the onset of ERT: in 4 patients with MPS II — after the first infusion of idursulfase, in 1 patient with MPS II — after 1 month of idursulfase therapy, in 1 patient with MPS II — after 3 months of ERT, in 1 patient with MPS II — after 5 months of ERT, in 1 patient with MPS VI — after 6 months of ERT); ** — after 27 months (14; 41), min — 1, max — 90 months of ERT; *** — the exceedance of the upper limit of normal for the corresponding age by GAGs values of patients with MPS (for an example of calculation, see *Methods*). MPS —- mucopolysaccharidosis, ERT —- enzyme replacement therapy, GAGs — glycosaminoglycans.

Table 2. GAGs excretion rates in children with MPS II who started to receive ERT at the age under and above 60 months

Indicators	**ERT onset**		***p***
	Under 60 months ***n* = 11***	**Above 60 months** ***n* = 8****	
Age of ERT onset, months	36 (28; 50)	99 (70; 149)	0.001
Duration of ERT, months	27 (8; 64)	29 (24; 41)	1.000
Normalized GAGs excretion (initially), %[#]	398 (253; 791)	448 (209; 953)	0.934
Normalized GAGs excretion (on ERT), %[##]	94 (0; 146)[§]	22 (0; 203)[§§]	0.837

Note. * — 8 patients of them with a severe form, 3 — with a mild form, ** — 7 patients of them with a severe form, 1 — with a mild form; [#] —- the time point corresponding to the time of the first urine sampling to determine GAGs excretion, [##] – after the period specified for the Duration of ERT indicator; [§] — $p = 0.003$, [§§] — $p = 0.05$ as compared to the initial value of the indicator. MPS — mucopolysaccharidosis, ERT — enzyme replacement therapy, GAGs — glycosaminoglycans.

Table 3. Dynamics of EchoCG indices in the course of ERT in children with MPS type I, II and VI

Indicators	**Before ERT*** ***n* =31**	**On ERT**** ***n* =31**	***p***
Regurgitation, degree			
• On the aortic valve	0 (0; 1)	1 (0; 2)	0.005
• On the pulmonary artery valve	0 (0; 1)	0 (0; 0)	0.638
• On the mitral valve	1 (1; 2)	2 (1; 2)	0.179

• On the tricuspid valve	1 (0; 1)	0 (0; 1)	0.616
IVS thickness, %[#]	1 (0; 27)	8 (0; 15)	0.657
PLVW thickness, %[#]	0 (0; 17)	9 (0; 20)	0.269

Note. * — in 4 patients, the first examination was performed after the onset of ERT (in 1 patient with MPS II after 1 month of ERT, in 1 patient with MPS I/II, and 1 patient with MPS II after 2 months, in 1 patient with MPS VI after 4 months of ERT); ** — median ERT duration of 32 months (18; 44), min — 4 months, max — 91 months; [#] — exceedance of the upper limit of normal by weight (in %). MPS — mucopolysaccharidosis, ERT —– enzyme replacement therapy, EchoCG — echocardiography, IVS — interventricular septum, PLVW — posterior left ventricular wall.

Table 4. Comparison of the regurgitation dynamics on heart valves and the dynamics of IVS and PLVW thickness in patients with MPS II who started to receive ERT at the age under and above 60 months

Indicators	**ERT onset**		***p***
	Under 60 months ***n* =14**	**Above 60 months** ***n* =10**	
Age of ERT onset, months min−max	35 (20; 46) 6−54	93 (70; 119) 65−176	0.001
Duration of ERT, months min−max	27 (7; 61) 4−75	35 (21; 44) 4−91	0.845
Regurgitation on the aortic valve: • Before ERT • On ERT • Change	 0 (0; 0) 0 (0; 1)* 0 (0; 1)	 0.5 (0; 2) 1 (1; 2) 0 (0; 1)	 0.043 0.033 0.977
Regurgitation on the pulmonary artery valve • Before ERT • On ERT • Change	 0 (0; 1) 0 (0; 0) 0 (-1; 0)	 0 (0; 1) 0 (0; 1) 0 (-1; 1)	 0.977 0.364 0.558
Regurgitation on the mitral valve • Before ERT • On ERT • Change	 1 (0; 1) 1.5 (1; 2) 0 (0; 1)	 2 (1; 2) 2 (1; 2) 0 (-1; 1)	 0.208 0.306 0.930
Regurgitation on the tricuspid valve • Before ERT • On ERT • Change	 0 (0; 1) 0 (0; 1) 0 (-1; 0)	 1 (0; 2) 1 (0; 2) 0 (-1; 1)	 0.640 0.033 0.292
IVS thickness: • Before ERT • On ERT • Change	 0 (0; 1) 2 (0; 15) 2 (0; 15)	 37 (19; 38) 6 (0; 11)** -25 (-31; 0)	 0.004 0.953 0.011
PLVW thickness: • Before ERT • On ERT • Change	 0 (0; 2) 2 (0; 11) 2 (-2; 11)	 9 (0; 48) 9 (0; 17) 0 (-14; 9)	 0.169 0.396 0.362

Note. In the group of patients who started ERT at the age under 60 months, there were 10 patients with a severe form and 4 with a mild form of MPS II; in the group of patients who started ERT at the age above 60 months, there were 9 patients with a severe form and 1 with a mild form of MPS II. Values of IVS and PLVW sizes are calculated as % exceedance of the upper limit of normal by weight. * — $p = 0.043$; ** — $p = 0.024$ as compared to the initial value of the indicator. IVS — interventricular septum, PLVW — posterior left ventricular wall, MPS — mucopolysaccharidosis, ERT —— enzyme replacement therapy.