Regular Article

Ten years of enzyme replacement therapy in paediatric onset mucopolysaccharidosis II in England


ARTICLE INFO

Keywords:
Mucopolysaccharidosis II
Hunter syndrome
Enzyme replacement therapy (ERT)
Idursulfase
Paediatric

ABSTRACT

The outcome of 110 patients with paediatric onset mucopolysaccharidosis II (MPS II) since the commercial introduction of enzyme replacement therapy (ERT) in England in 2007 is reported.

Median length of follow up was 10 years 3 months (range = 1 y 2 m to 18 years 6 month). 78 patients were treated with ERT, 18 had no ERT or disease modifying treatment 7 had haematopoietic stem cell transplant, 4 experimental intrathecal therapy and 3 were lost to follow up. There is clear evidence of improved survival (median age of death of ERT treated (n = 16) = 15.13 years (range = 9.53 to 20.58 y), and untreated (n = 17) = 11.43 y (0.5 to 19.13 y) p = .0005). Early introduction of ERT improved respiratory outcome at 16 years, the median FVC (% predicted) of those in whom ERT initiated < 8 years = 69% (range = 34 – 86%) and 48% (25 – 108) (p = .045) in those started > 8 years. However, ERT appears to have minimal impact on hearing, carpal tunnel syndrome or progression of cardiac valvular disease. Cardiac valvular disease occurred in 18/46 (40%), with progression occurring most frequently in the aortic valve 13/46 (28%). The lack of requirement for neurosurgical intervention in the first 8 years of life suggests that targeted imaging based on clinical symptomology would be safe in this age group after baseline assessments. There is also emerging evidence that the neurological phenotype is more nuanced than the previously recognized dichotomy of severe and attenuated phenotypes in patients presenting in early childhood.

1. Introduction

Mucopolysaccharidosis type II (MPS II; Hunter syndrome; OMIM 309900), is a rare X-linked disorder where deficient activity of the lysosomal enzyme Iduronate-2-sulphatase results in a progressive multi-system life-limiting disorder. Symptoms range from the typical facial coarsening and hepatosplenomegaly to skeletal, respiratory, auditory, cardiac and both central and peripheral nervous system dysfunction [1]. The basis of the disease lies in the pathological cascades resulting from the accumulation of various species of the inadequately metabolised glycosaminoglycans (GAGs) dermatan and heparan sulphate [2,3].

Originally the clinical phenotype was divided into two main subgroups, dependant on the presence (severe) or absence (mild, now termed attenuated) of neurological impairment [4,5]. The utility of this classification lies in its predictive power, for while respiratory impairment is the predominant cause of mortality in all, the life expectancy of those deemed neurologically impaired is significantly shorter [6]. Subsequent studies seeking to delineate the progression of neurological impairment [7] and the cognitive impact of disease in attenuated
patients [8] have added weight to the paradigm of two distinct populations. However, some authorities have suggested a broader neurological spectrum [9], a view that would appear to be consistent both with the typical nature of genetically inherited conditions and historical radiological evidence [10].

The advent of enzyme replacement therapy (ERT), used to treat the somatic manifestations of the disease [11], has resulted in improved survival [12] with short term positive impact demonstrated principally on cardiovascular and respiratory outcomes [13]. ERT has been available commercially in England since 2007, being offered to all patients with a biochemically confirmed diagnosis of MPS II, unless deemed too sick with such advanced disease that there is little prospect of benefit, or who have undergone successful haematopoietic stem cell transplant (HSCT). Historically paediatric MPS II patients in the UK have not undergone HSCT given the poor balance of risk and potential benefit seen [14]. However, the overall improvement in mortality seen in HSCT in lysosomal disease [15] and increasing indications of efficacy in MPS II [16,17] has meant that it is on occasion being offered to patients diagnosed under the age of 1 year i.e. predominately those with a prior family history. For paediatric patients in England, ERT is provided as part of multidisciplinary care in by 3 nationally commissioned centres, whose follow up has been uniformly directed by national agreed protocols (www.webarchive.org.uk/wayback/archive/20130325153351/ http://www.specialisedservices.nhs.uk/library/23/Guidelines_for_Mucopolysaccharidosis_Type_II.pdf). All investigations were performed annually, with the 6 minute walk and spirometry performed in all patients whose compliance allowed an accurate test to be performed. This retrospective study aims to review the impact of enzyme replacement therapy on paediatric MPS II patients to document the evolving nature of the problems faced by this cohort of patients. We also consider if there is a broader neurological phenotypic spectrum than previously described.

2. Methods and materials

2.1. Data collection

A retrospective audit of the survival and outcomes of paediatric patients treated in England between 2006 and 2016 was performed. This governmentally-mandated review involved all 3 nationally designated paediatric treatment centres, who initially jointly generated the data collection proforma (see supplemental data) and subsequently collected the anonymised data with local institutional approvals. Growth, school outcome and genotypic data were additionally collected by further retrospective medical note review in 2017 by each clinical team.

2.2. Inclusion criteria

All paediatric patients with an enzymatically confirmed diagnosis of MPS II who were reviewed between 2006 and 2016 at any of the 3 designated centres were included. Patients were followed until either death or transition to adult services (typically between 16 and 18 years of age, though in some more historical patients when transition age was less formalized, the last review prior to the age of 21 was used.)

2.3. Cardiac data

Available echocardiographic data were reviewed. Reduction in cardiac function was defined as the need for angiotensin converting enzyme (ACE) inhibition or reduced fractional shortening < 30%.

2.4. Neurological definition and data collection

In an attempt to more fully describe the neurological outcomes and given the lack of uniformity of psychological testing, the patient cohort was divided into 4 categories dependant on their school attainment. This categorisation was inherent to the UK Special Educational Needs Act of 2001 which promotes an inclusive ideal where by children are supported to stay at standard educational institutions. However, if the level of their disability is deemed too severe, they should be schooled at a more specialized institution specific for their needs. Thus, the cohort was divided into those who were at mainstream school without/with additional support and those at an institution of special educational needs with or without progressive neurological decline. For the purpose of this classification, progressive neurological decline is defined as the onset of seizures and/or the need for gastrostomy feeding due to impaired swallow or oral intake. Where available the Wechsler Intelligence Scale for Children (WISC-IV) scores were also collated. Those patients enrolled in the experimental intrathecal ERT trial or who had undergone HSCT were not included in the neurological outcome review.

2.5. Antibody testing

All antibody testing was performed by Shire, Lexington, MA, USA.

2.6. Statistical analysis

Kaplan Meier, Mann Whitney and Kruskal-Wallis analysis where appropriate were used for statistical analysis. A P value of < 0.05 was taken to be statistically significant. Statistical analysis was performed on IBM SPSS Statistics 23.0.

3. Results

The records of all 110 patients with confirmed isolated enzymatic deficiency in iduronate sulphatase activity, identified, were reviewed. All patients on ERT were treated with recombinant I2S (Idursulfase), Elaprase® (Shire, Lexington, MA, USA) at a dose of 0.5 mg/kg weekly.

3.1. Follow up

The patients' sub-stratification by treatment is shown in Fig. 1. The median length of overall follow up was 10 years 3 months (range = 1 y 2 m to 19 years 4 months). The median follow up of patients on ERT excluding those with additional intrathecal therapy or subsequent HSCT, was 11 years 1 month (range = 1 y 3 m to 19 years 4 m), with the median length of exposure to ERT being 9.36 years 4 months (range = 2 months to 17 years 9 m). The median follow up of those not started on ERT was 9 y 3 m (range = 1 y 6 month to 19 y 4 months).

In the 78 patients who were started on ERT, the median onset of ERT was 6 years 7 months (range < 1 month to 16 years). Those who were diagnosed pre-license (n = 31) were commenced on ERT later than those diagnosed subsequently (n = 47) (median = 8.73 years v 3.01 years respectively (p < .0001)).

3.2. Genotype

In the 87 patients for whom the genotype was available, missense variants were the commonest pathological variants found, present in 40/87 (46%). Four previously undescribed pathogenic variants were found, (3 missense: c.685C > G p. (His229Asp), c.1204G > A p. (Glu402lys), c.269C > T p.(Ser90Phen) and an insertion c.1528insT). All four variants were predicted to be pathogenic by in silico analysis and all patients had significantly reduced iduronate sulphatase levels. The phenotype for the first two missense variants is unclear as the patients were still under 4 years of age. However, the patients with the latter two variants are now 16 and 17 years old, respectively. While both have some intellectual impairment requiring additional educational support, neither have neurological regression, nor require or have required any medical interventions beyond carpel tunnel surgery.
3.3. Age of diagnosis

Overall the median age of diagnosis of probands (i.e. excluding those with a prior family history) was 2 y 8 m (range = 3 m — 15 y 9 m). Those diagnosed prior to the advent of commercially available ERT were diagnosed at the median age of 3.17 years (range = 0.25 y — 9.16 years) whereas those diagnosed post 2007 were diagnosed at median age 2.5 years (range = 0.16 y — 15.5 years) \( p = .01 \). Sub—analysis dividing into historic 5-year cohorts (see supplementary data) showed a significantly earlier diagnosis in the 2005—2009 cohort (median 1.58 years) compared to the other cohorts but no continuing trend towards overall improvement in age at diagnosis with the passage of time.

3.4. Survival

The survival of the overall cohort, excluding those that underwent potential neurological modifying therapy i.e. HSCT or intrathecal therapy, determined by Kaplan-Meier analysis at 21 years was 42%. Thirty-three patients died during follow-up period (16/78 (20.5%)) of those who received ERT and 17/18 (94.4%) of those who never received ERT. The predicted survival at 21 years of those only treated with peripheral ERT was 52%, and those not treated was 9% \( p < .001 \) (Fig. 2).

Considering only those patients who died, overall median age of death was 13.7 years (range 0.5 years — 20.6 years). Median age of death in those who never received ERT was 11.48 years (range 0.5 to 19.17 years) compared to 16.67 years (range 9.58 years to 20.58 years) for those treated with ERT, (difference between groups \( p < .0001 \)) (Fig. 3). There was no significant difference between these groups in age at diagnosis or baseline cardiac function and both groups had similar genotypes.

In 13 of the 17 where cause of death was available, either acute or chronic respiratory impairment was the principle cause of death. Other causes included non-accidental injury and acute cardiac arrhythmias.

Thirteen patients had their ERT discontinued. In 10 this was due to disease progression and in the others because the burden of treatment was felt to outweigh the benefits despite the lack of overt disease progression. The median survival after stopping ERT was 3 years (range = 0.25—6.58 years) in 11 of these. Two continue to be alive post ERT withdrawal. The first of these, despite neurological progression which underlaid the ERT withdrawal, is still alive 8 years after cessation. The other, whose treatment was stopped due to lack of overt improvement, remains alive 4 years after cessation. Both of these patients are continuing to have full cardiac, respiratory and ENT symptomatic management as required.

3.5. Urinary glycosaminoglycans (GAGs) and serum antibodies

Urinary GAG analysis was performed in three different laboratories and was therefore not standardised. The median reduction in total urinary GAGs when examining GAG/creatinine ratio from baseline to latest sample was 53.2% (\( n = 11 \)), 72.9% (\( n = 25 \)) and 80.8% (\( n = 36 \)) respectively in the 3 centres. Overall 7 patients showed an increase in urinary GAGs. Of these, 2 were not given ERT, 4 had persistent anti-ERT serum antibody titres > 6400, and antibody was unavailable for one patient.

In all, 40 patients had results from antibody testing with 21/40 never developing an anti-drug IgG response. In the 19 patients positive for antidrug IgG antibodies, 7 subsequently seroconverted within the first 6 months of ERT, with none of these having a titre > 1 in 200. Of the 16 patients that died despite being started on ERT, 6 were tested for antibodies, of these all had persistent antibody titres between 100 and 12,800.
3.6. Surgery

Major surgical interventions were limited in this cohort. 4/90 (4.4%) required ventriculoperitoneal (VP) shunting for hydrocephalus (age range = 9–15 years).

In 3 of these patients, the VP shunt was performed to attempt to reverse progressive visual impairment, with improvement observed in 2. These 3 individuals did not have overt signs of hydrocephalus or raised intracranial pressure on MRI scanning performed prior to the onset of visual loss in any of the 3. The other patient was asymptomatic but radiologically showed progressive triventricular hydrocephalus.

3/90 (3%) had lumbar spinal surgery, with 2 patients having surgery at < 10 years of age and one at 14 years of age. One patient with progressive neurological disease displayed signs of clinical and radiological myelopathy prior to lumbar surgery, with both pain and gait improving immediately after surgery.

No patients in this cohort underwent cervical spine surgery. Of the 67 patients where data was available, 28 (43%) had undergone carpal tunnel surgery with the median age of initial surgery being 6.25 years (range = 4 to 16 years).

3.7. Cardiology

The commonest cardiovascular manifestation was mitral valve disease (see Table 1) with 35/58 (60%) of patients having some degree of mitral valve involvement at baseline, median age = 3 years (range = 10 m to 9.16 y), while 53/70 (75%) demonstrated mitral valve involvement at last review, median age = 12.68 years (range = 1.25 to 18.5 y).

While the baseline cohort tended to show left ventricular hypertrophy (LVH) but normal function the older cohort had minimal LVH but worse function.

Longitudinal data was available for 46 patients where median age of follow up was 11.53 y (range = 2 months to 19.58 y). Six patients had a degree of left ventricular hypertrophy at baseline, in all these had resolved at the time of last review (range of follow up 14 months to 13 years 9 months). Overall valvular disease was noted to have progressed in 18/46 (40%), 9 (19.5%) showing progression of their mitral valve disease, while 13 (28%) had progression of the aortic valvular disease. The length of follow up was not significantly different in patients whose mitral valve disease progressed, median follow up 12y 8 m 9 (range 0.33 to 19.58 y) when compared to those that without progression of valve disease (median follow up of 11.33 y (range 0.25 to 18.5 y)). Excepting 1 patient with mitral valve disease progression, all patients had ERT. One patient underwent aortic valve replacement at the age of 18 years during follow up. While ECGs were not part of the audit data, one death was presumed secondary to a cardiac arrhythmia.

3.8. Neurology

The patients were divided into 4 groups depending on both overt neurology and schooling level obtained (see Table 2). Of the 96 patients who had neither HSCT or intrathecal therapy, 6 had not reached the age of formal schooling during this study. The educational level was known in 79 of the remaining 90 patients. 8% were in mainstream school with no educational assistance, 23% required additional assistance in mainstream school, 35% were educated in a special needs environment, and 34% were classified as having progressive central neurological involvement or regression of skills.

Overall hearing impairment requiring hearing aids occurred in 46/79 (58%) patients (age of onset 2–9 years). In the 69 patients whose neurological outcome was known, those with progressive neurological disease were significantly more likely to need hearing aids. There was no difference in hearing aid use in those diagnosed pre-licencing of ERT compared to those born subsequently.

3.9. Growth

A cross-sectional review of growth was obtained from the cohort’s latest weight and height measurements were examined (see Supplementary data). The patients up to 10 years of age, who have been on ERT since diagnosis, tended to fall within the normal range for heights but in general have a weight that is at least one centile greater than their height. With the exception of 2 patients, those over the age of 10 years appear to have failed to mount an adequate pubertal growth spurt, the height of the majority of those over ten being less than the 4th centile in comparison to their weights which were principally between the 9th and 50th centiles with commensurately high body mass indexes (BMIs). In those classified as neurologically affected, BMI was significantly higher (median BMI = 90th centile v 80th centile respectively, p = .001).

3.10. Ambulation and respiratory

Lung function assessments by spirometry was available in 33 patients. 24 patients treated with ERT were over 16 years at time of last assessment; this cohort did not differ in median age of diagnosis from the overall cohort (p = .101). The predicted FVC based on height and weight was < 60% in 9/24 with decline typically seen in the mid-teens. In this cohort those started on ERT prior to the age of 8 (n = 11) had a median last FVC of 69% predicted (range = 34–86%), while those started after 8 (n = 13) had a last median FVC of 48% (range = 25–108%), p = .045.

In four patients who had not yet reached 16 years of age there had been a drop of > 5% predicted FVC on serial measurements, while in
the other 5 patients FVC remained stable.

All 5 patients with FVC < 30% of predicted had a tracheostomy and subsequently died 3–7 years post tracheostomy. Overall, the median age of insertion of tracheostomy was 11 years 3 months (range 7.83 to 14.08 years). Despite requiring a tracheostomy none of the patients required active ventilatory support. One patient had a FVC of 54% prior to aortopexy and tracheal reconstruction at the age of 19 years.

18 of the 24 patients followed until at least 16 years of age demonstrated improved 6 minute walk test over the period of review. In all these patients the baseline was within 6 months of their seventh birthday. The median improvement from baseline was +67 m (17.2%) (range -129 m to +292 m, −26 to +52%). Serial 6MWT for at least 3 years from baseline was available in 6 other non-neurologically progressive patients who had not reached the age of 16 and showed a median gain of 6% (range -87 m to +197, −27% to 70%).

4. Discussion

This retrospective study is the largest non-commercial reported cohort of paediatric MPS II patients. In keeping with recently published cohorts [12,13] it demonstrates the positive impact of ERT on the overall survival in MPS II. It also highlights both the evolving cardiac phenotype and the apparently low levels of major neurosurgical and spinal interventions needed. However, it does also document the areas of apparent unmet need with ERT appearing to have minimal impact on such somatic features as hearing and carpal tunnel syndrome.

This cohort provides support for the concept of a broader range of central neurological involvement existing outside the existing paradigm of the duality of severe and attenuated disease. The weaknesses inherent in the design of this retrospective study are the limited data available for growth and respiratory assessments.

The overall survival of this cohort of 48% at 20 years differs from that of the Hunter Outcome Study (HOS) registry [6], most likely due to the differing ages ranges covered (HOS encompasses some later onset patients). The improvement in overall survival seen in those treated with ERT would however be in keeping with that seen in the HOS data [12]. However, where survival does seem to differ most markedly from the recorded literature [18,19] is in those patients where ERT was discontinued, with previous literature highlighting a dramatic rapid decline across multiple domains on ERT cessation. In this cohort, in the 13 patients here where ERT was withdrawn, few displayed altered clinical manifestations in the months immediately after withdrawal and survival for > 4 years was noted in 2 patients. The differing experiences are possibly explained by the timing of the discontinuation of ERT. In this cohort this occurred when the severity of the neurological or somatic disease was such that the burden of therapy clearly outweighed any potential benefits i.e. withdrawal was at an advanced stage of disease. In the previously reported Polish cohort where dramatic decline was noted, ERT withdrawal was enforced due to funding constraints [18]. Those patients were clinically stable patients i.e. likely to be less symptomatic and therefore a reduction in clinical status is easier to demonstrate. It is also to be noted that in all 6 out of the 13 patients who were tested in this study, there was a mild to modest persistence of IgG antibodies, which has previously been suggested to [20] have reduced the efficacy of ERT. Data from this cohort supports recently published work linking IgG production and failure to resolve urinary GAGs, which would infer reduced efficacy [21,22].

The overall improvement in survival may in part be due to the impact on the respiratory system. This cohort suggests that earlier institution of ERT improves predicted FVC at 16 when compared to later onset of ERT. This would be in keeping with previous trial data which showed a trend towards improvement in FVC [11] and Hunter Outcome Survey (HOS) data which showed an increase in absolute FVC over 3 years [13]. It is to be noted that while this series of patients did show an overall increase in absolute FVC (data not shown) they did show a decrease in predicted FVC especially in the second decade. Predicted

| Cardiac manifestations comparing original baseline line and latest cardiology review. |
|---------------------------------|---------------------|---------------------|
| Baseline n = 58. Median age 3 y (range = 10 m to 9 y 2 m) | Latest echo n = 70 | |
| MR | MR | MR | MR |
| 35 (60%) | 30 (52%) | 5 (14%) | 26 (45%) |
| 24 (41%) | 28 (47%) | 7 (20%) | 18 (33%) |
| MR = Mitral Regurgitation, LHV = Left Ventricular Hypertrophy, TR = Tricuspid Regurgitation. | 10 cases of mild LVH | Reduced function | 5 reduced LVH | 1 LVH |
FVC was felt a better overall measure in this group given the potential impact of growth. Certainly, the restriction of MPS II on growth is well documented with a typical failure to maintain growth velocity after the age of 8 years [23]. Indeed the positive impact on growth may well be one of the more important effects of ERT and indeed be behind the perceived improvement noted in siblings [24]. It may also explain why no effect was seen in smaller non registry studies [25,26], given the older age of ERT onset in a significant number of those patients. Due to the cross-sectional growth data obtained, the real impact of ERT on growth could not be examined here. The overall character of the growth curves are in keeping with previous studies, with height velocity maintained until the age of 8 years and those with a neurological phenotype having a higher BMI [23].

This cohort also highlights the degree and evolution of cardiac disease seen in childhood onset MPS II despite the use of ERT. Although the resolution of left ventricular hypertrophy was in keeping with previous studies, with height velocity maintained until the age of 8 years and those with a neurological phenotype having a higher BMI [23].

Finally, one of the more intriguing aspects of this cohort is that of the neurological outcome. The accepted paradigm is that patients fall into one of two subtypes, those in whom cognition plateaus at 48–55 months with subsequent rapid decline [7] or those whose IQ falls within the normal range, albeit with subtle attention defects [8]. However, the perceived experience of some of the authors prior to this study was that not all patients fall easily into this binary classification, with some having clear intellectual impairment without overt rapid regression. Attempts to examine this retrospectively are difficult, given lack of uniformity in psychological/developmental follow up. In an attempt to address this, the degree of educational support was reviewed. This classification does recapitulate the expected UK ratios of attenuated (i.e. Groups A + B = 29% to severe (Groups C + D, 71%) disease [4,27]. It also reproduces the 2 classical recognized cohorts i.e. those with normal intellect, seen here as the Groups A + B, and those that undergo the progressive neurological decline, Group D. However, it does suggest a third grouping of patients that have some intellectual impairment but who do not obviously develop the progressive neurological progression, i.e. Group C. From the data available, this group would include patients who would seem to fall into the limited support and intermediate support groups on the Supports Intensity Scale, unlike those in groups B or D [37]. The SIS is the best validated assessment tool that looks at disability in terms of degree of support received by the patient [38]. For advocates of the binary division of neurological outcome in MPS II, the most logical explanations are that Group C are either those patients that are yet to yet to undergo neurological regression or misclassified attenuated patients. Thus, it is important to note that there is no significant difference in length of follow up (p = .235) between Groups C and D and that Group C is of an average age greater than that where neuro-regression would have been
predicted to occur [7]. Equally, group C is unlikely to contain too many attenuated patients given the previously nationally recognized ratios of severe and attenuated patients [4,39,40]. While the paucity of DQs available for Group C means that at best this data is only suggestive of a broader neurological phenotype, the recognition of the possibility of a more heterogenous neurological phenotype is potentially crucially important. If true it potentially impacts both on the counselling of families, where impaired cognition may be mistaken for advent of neuro- logical progressive disease, and also on potential clinical trial design. In the latter, unless the variability in decline is recognized the impact of interventions could be potentially under or overestimated, and a single DQ score at a young age cannot be taken to reliably predict neurode- velopment prognosis.

In conclusion this cohort supports prior evidence that ERT does improve overall survival in MPS II, with the respiratory data indicating that the earlier the initiation of ERT, the better the outcome. However, this improvement in survival does seem to be creating a cohort of pa- tients with increasing valvular heart disease, while not obviously im- pacting on some clinically important aspects of somatic disease such as the need for hearing support or carpal tunnel surgery. Finally, this co- hort does also suggest that the neurological phenotype is wider than previously realized. The potential of this heterogeneity of neurological impact should be the subject of greater research, as without this, the true impact of future neurologically targeted therapy will be uncertain.

Declaration of Competing Interests
SR, CS, EJ, SS, JD, JR, PH, CB declare no conflicts of interest. AC has received institutional research grants from Shire/Takeda. UR has research, educational and travel grants from Genzyme, Shire/Takeda, Amicus. AB has received educational and travel grants and consultancy fees from Sanofi, Shire/Takeda and Biomarin and institutional research grants from Shire/Takeda and Sanofi. MC has received educational and travel grants from Shire/Takeda and institutional research grants from Shire/Takeda. JD has received travel and educational grants for Biomarin, Shire/ Takeda, Actelion and Sanofi. VS has received an institutional research grant from Shire/Takeda. BS has received an institutional research grant from Sanofi. SJ has received educational travel and institutional grants from Shire/Takeda, has received Honoria for consultancy for Denali and Regenbio. He is also a Scientific advisory board member and stock- holder of Orchard Therapeutics. Excepting SJ, none of the authors own stocks or shares in any pharmaceutical companies.

Funding
This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Appendix A. Supplementary data
Supplementary data to this article can be found online at https://doi.org/10.1016/j.ymgme.2019.07.016.

References
[22] A. Pano, et al., Immunogenicity of idursulfase and clinical outcomes in very young patients (16 months to 7.5 years) with mucopolysaccharidosis II (Hunter syn- drome), Orphanet. J. Rare. Dis. 10 (2015) 50.