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Intrathecal enzyme replacement for cognitive decline in mucopolysaccharidosis type I, a randomized, open-label, controlled pilot study

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Abstract

Central nervous system manifestations of mucopolysaccharidosis type I (MPS I) such as cognitive impairment, hydrocephalus, and spinal cord compression are inadequately treated by intravenously-administered enzyme replacement therapy with laronidase (recombinant human alpha-L-iduronidase). While hematopoietic stem cell transplantation treats neurological symptoms, this therapy is not generally offered to attenuated MPS I patients. This study is a randomized, open-label, controlled pilot study of intrathecal laronidase in eight attenuated MPS I patients with cognitive impairment. Subjects ranged between 12 years and 50 years old with a median age of 18 years. All subjects had received intravenous laronidase prior to the study over a range of 4 to 10 years, with a mean of 7.75 years. Weekly intravenous laronidase was continued throughout the duration of the study. The randomization period was one year, during which control subjects attended all study visits and assessments, but did not receive any intrathecal laronidase. After the first year, all eight subjects received treatment for one additional year. There was no significant difference in neuropsychological assessment scores between control or treatment groups, either over the one-year randomized period or at 18 or 24 months. However, there was no

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significant decline in scores in the control group either. Adverse events included pain (injection site, back, groin), headache, neck spasm, and transient blurry vision. There were seven serious adverse events, one judged as possibly related (headache requiring hospitalization). There was no significant effect of intrathecal laronidase on cognitive impairment in older, attenuated MPS I patients over a two-year treatment period. A five-year open-label extension study is underway.

Keywords

Mucopolysaccharidosis; lysosomal disease; intrathecal enzyme replacement therapy; Hurler; glycosaminoglycan; cognitive decline

1. INTRODUCTION

Mucopolysaccharidosis type I (MPS I) is a lysosomal disorder caused by mutations in the *IDUA* gene, resulting in greatly reduced or null activity of the alpha-L-iduronidase enzyme. Alpha-L-iduronidase is a soluble lysosomal hydrolase that is involved in catabolism of heparan sulfate and dermatan sulfate glycosaminoglycans. Abnormal glycosaminoglycan accumulation within cells contributes to progressive disability and disease in multiple organ systems, including the brain. There is a spectrum of disease severity in MPS I, which has historically been classified as Hurler syndrome, the most severe phenotype, to Scheie syndrome, the least severe phenotype. Intermediate disease is described as Hurler-Scheie syndrome [1]. About forty percent of patients with MPS I have Hurler-Scheie and Scheie syndromes, which are referred to collectively as attenuated MPS I [2, 3].

Patients with Hurler syndrome develop the most severe disease of the central nervous system, which includes progressive cognitive decline resulting in significant intellectual disability by the age of three years [3, 4]. Hematopoietic stem cell transplantation has been found to prevent the precipitous cognitive decline if performed early, usually before the age of two years [5]. Patients with attenuated forms of MPS I can also experience cognitive impairment, though not as early as in Hurler syndrome. Younger attenuated MPS I patients, between the ages of two to six years, generally have normal intelligence. There is a wide range of intellectual ability in older attenuated MPS I patients. In the six to twenty-five year age range, 43% of patients have either borderline or impaired cognitive ability [6, 7]. Some attenuated MPS I patients appear to experience cognitive decline in the range of one standard deviation of loss of IQ points over ten years [8]. Although the primary defect in MPS I is a catabolic defect of glycosaminoglycan metabolism, the factors underlying the progressive disease symptoms and particularly the progressive central nervous system disease are incompletely understood [9]. Factors, in addition to direct brain disease, which may affect cognitive decline in these patients include the development of hydrocephalus, vision and hearing loss, and the severity of physical disease, as well as inflammatory processes and other pathogenic cascades [10]. Attenuated MPS I patients are generally not candidates for hematopoietic stem cell therapy, due to age at diagnosis, severity of disease, and high risk of the treatment [11].

Current treatments for attenuated MPS I patients include enzyme replacement therapy (ERT), which is approved for use in human patients as laronidase (recombinant alpha-L-

iduronidase) via weekly intravenous injections. Although intravenous ERT addresses many of the physical symptoms of the disease, insufficient enzyme crosses the blood-brain barrier to have a significant impact on the central nervous system manifestations of MPS I [12]. Enzyme replacement therapy given intrathecally has been shown to achieve greater than 20-fold normal levels of iduronidase and reduce glycosaminoglycan storage in the brain, spinal cord, and spinal meninges in the canine model of MPS I [13]. There is limited human experience with intrathecal enzyme replacement therapy. A pilot study of five MPS I patients with spinal cord compression demonstrated safety of the procedure and subjective improvements in spinal cord compression symptoms [14]. Several Hurler syndrome patients have been treated with intrathecal enzyme replacement in combination with hematopoietic stem cell transplantation [15]. A few patients have received intrathecal ERT under individual investigational new drug applications (INDs), including a young adult with attenuated MPS I who was reported to have improvements in memory testing and school performance after twenty-four months of treatment [16].

We designed this study to evaluate the safety and efficacy of repeated intrathecal laronidase administrations to affect cognition in attenuated MPS I patients. The study had a randomized controlled period of one year, where we evaluated all subjects with neurological evaluations, laboratory testing, neuropsychological testing, and quantitative magnetic resonance imaging (qMRI).

2. MATERIALS AND METHODS

2.1 Subjects

All study procedures were reviewed and approved by the John Wolf Human Subjects Committee at the Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center (LA BioMed) and at institutional review boards at UCSF Benioff Children's Hospital Oakland and at the University of Minnesota. The study was part of the Lysosomal Disease Network, a clinical research consortium among the National Institutes of Health's Rare Diseases Clinical Research Network (RDCRN). The study was conducted in the United States under a Food and Drug Administration Investigational New Drug (IND) application and it was listed on www.clinicaltrials.gov (National Clinical Trials (NCT) number 00852358). In order to be eligible, subjects had to be age six years or older with MPS type I, and have evidence of cognitive impairment, which was defined as a score of at least one standard deviation below the mean on IQ testing or in one domain of neuropsychological function. One standard deviation is an accepted cutoff in neurocognitive measurement for defining abnormalities of function [7, 15, 17]. For neurocognitive testing, the qualitative ranges include: average range (−1 to +1 SD); below average (>−2 to <−1 SD below the mean) and impaired (<−2 SD). Further, attenuated MPS I patients likely would not show greater than two standard deviations below mean. For individuals with MPS I who do show this level of impairment, there is great risk that CNS complications have reached "the point of no return" in that therapy is not likely to be able to provide calculable, or clinically meaningful, cognitive benefit. Subjects were excluded if they had undergone hematopoietic stem cell transplantation, were unable to comply with study procedures, had significant lumbar pathology precluding access to the intrathecal space via lumbar puncture, or

significantly impaired spinal CSF flow as detected on a nuclear medicine flow study as part of screening.

Subjects were assessed and treated with study drug at two sites, LA BioMed and the UCSF Benioff Children's Hospital Oakland. All subjects received neuropsychological testing at the University of Minnesota, where they were also part of a longitudinal study of brain structure and function in the mucopolysaccharidoses.

2.2 Study design

This was a two-year pilot study of intrathecal laronidase in MPS I patients with cognitive impairment. The study was randomized and controlled during the first year, and then all subjects received treatment during the second year. Randomization was stratified by site and performed by a statistician at LA BioMed who was otherwise not involved in the study. Due to the need for anesthesia, sham lumbar punctures were not possible. Subjects as well as treatment investigators at LA BioMed and Children's Hospital Oakland were aware of treatment allocation, but subjects did not reveal treatment group to the neuropsychologists performing testing at the University of Minnesota, and neuropsychologists did not ask about treatment assignment as part of testing. The researchers who analyzed the brain MRI data were masked to treatment allocation.

During the first year of the study, treatment subjects received 4 monthly doses of 1.74 mg laronidase diluted in Elliott's B (Ben Venue Laboratories) artificial cerebrospinal fluid (1 part laronidase to 2 parts Elliott's B by volume; total volume 9 mL) administered intrathecally via a lumbar spinal injection. Then, they received one dose every 3 months thereafter (Table 1). Canine studies suggested a dosing interval of 3 months would be sufficient based on lack of GAG substrate reaccumulation at 3 months. A loading regimen of once monthly for four doses was suggested however, based on the rationale that reduction of GAG could require more frequent dosing, whereas a 3 month interval may be a reasonable "maintenance" regimen. Control subjects visited the study site at LA BioMed or Children's Hospital Oakland also monthly for 4 visits and then quarterly, on the same schedule as treatment subjects, but they did not undergo the treatment procedure. They received all other study assessments, however. At Month 12, all control subjects started receiving treatment on the same quarterly schedule as the treatment subjects.

2.3 Study intervention procedure

Subjects receiving laronidase were admitted to the hospital. The study treatment was performed in a procedure room or in a radiology suite if a fluoroscopic-guided lumbar puncture was necessary. Subjects had continuous monitoring and intravenous access. All subjects received local anesthesia with subcutaneous lidocaine 1%, and some subjects also received conscious sedation with intravenous midazolam and fentanyl. Opening pressure was measured with a standard manometer and approximately 6–10 mL of CSF was collected for laboratory evaluations. The laronidase was then injected over 2–3 minutes into the intrathecal space. After the procedure, subjects were taken back to their hospital room where they were on continuous monitoring overnight. They were discharged the day following the procedure if they did not have any new symptoms including headache greater than baseline.

In addition, 48 hours after the procedure, subjects returned for an outpatient visit, where an interim history and physical and neurological exam were performed.

2.4 Measures of safety

To evaluate the possible adverse effects of the treatment, physical and neurological exams were performed before and after every treatment, as well as 24 and 48 hours after every treatment. Blood and CSF were collected for routine chemistries, as well as anti-iduronidase IgG antibody analysis. Visual acuity was measured via Snellen test. All adverse events during the study period were recorded.

2.5 Objective measures of efficacy

The primary efficacy outcome measure was the Hopkins Verbal Learning Test, based on preliminary data showing that memory was differentially affected in Hurler-Scheie patients [8]. The entire neuropsychological battery was performed every six months and included tests of intelligence, attention, executive function, visual and verbal memory. Subjects were examined with the following tests: Wechsler Abbreviated Scale of Intelligence (WASI), Test of Variables of Attention (TOVA), Brief Visuospatial Memory Test (BVMT), Hopkins Verbal Learning Test (HVLT), and the Cambridge Neuropsychological Test Assessment Battery (CANTAB). All neuropsychological scores are reported as standard scores with a mean of 100 and a standard deviation of 15 from published normative data, if available. For some of the tests, norms for children less than age sixteen years were not available, and therefore standard scores could not be generated. For those tests, including the Hopkins Verbal Learning Test and the Brief Visuospatial Memory Test, raw scores were analyzed instead.

Other objective measures of efficacy included the following clinical, laboratory, and radiological tests. At every study visit, Functional Independence Measure (FIM) score and Six-Minute Walk Test were used to assess any changes in functional status. Cerebrospinal fluid glycosaminoglycans, collected at every treatment, were measured at Seattle Children’s Hospital using a clinically available test. The laboratory uses a dimethylene blue dye-binding assay to quantitate total glycosaminoglycans. Three of the treatment subjects had their Baseline and 12 month CSF sent to Duke University where glycosaminoglycans were analyzed using a tandem mass spectrometric method that targets methylated dimer products of methanolyzed chondroitin sulfate (CS), herparan sulfate (HS), and dermatan sulfate (DS), as previously described[18].

. Along with neuropsychological testing, MRI was performed at baseline, and then every six months. (Table 1) MRI of the brain was acquired on a 3T Trio Siemens scanner at both sites-- the Center for Magnetic Resonance Research (CMRR), University of Minnesota and for one subject who had a ventriculoperitoneal shunt, at the Neuroscience Imaging Center, UCSF Benioff Children’s Hospital Oakland. Details of MRI data acquisition are included in the supplementary materials.

2.6 Subjective measures of efficacy

Subjects and their caretakers were asked at baseline to report the most troubling symptoms related to cognitive impairment. At each visit, they were asked to rate these from baseline as 0 = no change, +1 = slightly better, +2 = moderately better, +3 = much better, −1 = slightly worse, −2 = moderately worse, or −3 = much worse. The investigator was also asked to record whether the subject was better, worse, or unchanged from baseline as an overall ("global") assessment using the same scale.

2.7 Data analysis

The safety and efficacy analyses included all enrolled subjects. The planned study size was sixteen subjects, which would provide 80% power to detect a mean difference in scores on the Hopkins Verbal Learning Test, the primary efficacy outcome, of 6 points. All of the neuropsychological tests were analyzed comparing the difference in change in scores from baseline to months 12, 18, and 24, adjusted for baseline scores using linear regression. Due to limited sample size available, model-based standard errors were used in conjunction with t-distribution and model degrees of freedom for confidence intervals and P-values. Means and standard deviations were also compared between baseline vs. month 12 and baseline vs. month 24 for all the neuropsychological tests. A p-value of less than 0.05 was considered statistically significant. Brain MRI volumes, fractional anisotropy, and mean diffusion values were compared between treatment and control groups.

3. RESULTS

3.1 Study population and characteristics

Screening and enrollment took place between December 2009 and August 2012. Table 2 shows subject demographics as well as the MPS I genotypes for each participant separated by group. Ten subjects were screened and eight were enrolled. The two subjects screened but not enrolled, one, because of inability to comply with study procedures and the other, due to impaired spinal CSF flow. Based on the inclusion criteria, there were subjects with normal intelligence but impairment in other domains, such as attention. Three of the eight subjects had intelligence quotients in the normal range. Because subjects with severe cognitive impairment and/or hematopoietic stem cell transplantation were excluded, all of the subjects had attenuated MPS I and none had Hurler syndrome. All subjects had received intravenous laronidase prior to the study over a range of 4 to 10 years, with a mean of 7.75 years. Weekly intravenous laronidase was continued throughout the duration of the study.

3.2 Safety, adverse events, and antibodies

Subjects experienced many unrelated adverse events during the study period and most were attributed to mucopolysaccharidosis type I. Table 3 lists all serious adverse events as well as adverse events that were thought to be possibly related to treatment, during the both the randomization period and the open-label period. Seven serious adverse events occurred in the subjects. One serious adverse event was deemed possibly related. The subject, a young adult female, had a severe headache 15 hours following the second dose of intrathecal laronidase. Her neurological examination was unchanged, but due to continuing pain, she

was kept in the hospital for additional 24 hours. The event was classified as serious due to the prolonged hospitalization. Other adverse events related to treatment include back pain at the site of injection, headache, groin pain, neck spasm, buttock pain, and transient blurry vision. There were several serious adverse events not related to treatment reflecting the large burden of disease experienced by these subjects.

Due to body habitus and spine abnormalities, repeated lumbar punctures were difficult, and eventually 7 out of 8 subjects required fluoroscopic-guided lumbar punctures. For one control subject during every treatment, interventional radiology accessed the lumbar cistern, but CSF did not flow out of the needle normally, so CSF could not be collected. That subject still received treatment.

One of the serious adverse events, spinal cord compression was a significant issue in this study. Two out of the eight subjects had already had cervical spinal decompression surgery years prior to the study. Seven out of the 8 subjects had hyperreflexia in all four limbs at baseline and this probably reflected low level asymptomatic spinal cord compression. Three subjects developed symptomatic spinal cord compression during the study and two of them required decompression surgery, which caused delay in treatment.

Anti-iduronidase IgG antibodies were measured at every study visit (Figure 1). All of the study subjects had been receiving intravenous laronidase for years prior to study entry. Anti-iduronidase titers were low for 6 of the 8 patients. For two of the subjects, the serum titers did rise above the level that was published as clinically “tolerant” based on preclinical data [19]. Of note these were the two subjects that required spinal cord decompression surgery during the study. There was no change in the study procedure due to the elevated titers.

3.3 Neuropsychological Tests

The primary efficacy endpoint was the difference in mean change in the total recall score on the Hopkins Verbal Learning Test between treatment and control groups at 12 months. There was no significant difference between groups at 12 months, 18 months, or 24 months (Table 4 and Fig 4). Nor was there a significant difference between treatment and control groups in any of the neuropsychological tests. Subjects in the control group did not experience any significant decline over the 12 month untreated period in any neuropsychological test except the Brief Visuospatial Memory Test, where the treatment group also experienced decline.

In the Wechsler Abbreviated Scale of Intelligence (Figure 2), there was a large range of intelligence quotients (IQ) among subjects. Generally individual IQ was stable from the beginning to the end of the study. However, verbal IQ showed an improvement in the treatment group but not the control group of 8.75 points in standard score (95% CI 0.61, 16.89; p=0.037) between 0 and 24 months.

Several of the subjects showed deficits in the Test of Variables of Attention at baseline (Figure 3). The D-prime measures rate of deterioration of performance over time. Neither group demonstrated significant improvement in either the D-prime score, Errors of Commission (a measure of impulsivity) or Errors of Omission (a measure of inattention). The Response Time Variability, a measure of consistency of response time, accounts for over

80% of the variance in the TOVA. Again, there were no significant changes over time in either group, although improvement in the Response Time Variability score of 28 points between 0 and 24 months in the control group did approach significance (95%CI −4.68, 60.68, p= 0.087).

The Hopkins Verbal Learning Test and Brief Visuospatial Memory Test (Figure 4) measure verbal memory and visuospatial memory, respectively. The HVLT total recall score (the primary efficacy outcome for the study) showed no significant difference in the change over time between treatment and control groups. However, the treatment group over the first twelve months did have a near significant increase in score of 4.75 points (95% CI −0.01, 9.51; p=0.050). The Brief Visuospatial Memory Test was the only test where many of the subjects in both groups experienced small declines. Declines were statistically significant between 0 and 24 months for both control and treatment groups in the BVMT Delayed Recall scores (Figure 4e–f). The control group declined by −3.73 points (95% CI −6.09, −1.38; p=0.005) and the treatment group declined by −2.75 points (95% CI −4.87, −0.63; p=0.016).

3.4 Cerebrospinal fluid analysis

Cerebrospinal fluid (CSF) glycosaminoglycan levels were obtained at each lumbar injection and assayed by a dimethylene blue dye method (Figure 5a). Three of the four treatment subjects started with baseline CSF glycosaminoglycan levels near or below the normal mean and the levels remained stable throughout the study. One treatment subject had an elevated CSF glycosaminoglycan level at the start of the study and experienced an approximately 50% reduction in levels during the study. Two of the four control subjects had elevated CSF glycosaminoglycan levels at baseline and the levels remained elevated. One of the control subjects never had CSF collected during study, as mentioned above in the Safety section. Three of the treatment subjects had their Baseline and 12 month CSF sent to Duke University where the glycosaminoglycans heparan sulfate, chondroitin sulfate, and dermatan sulfate were assayed with a mass spectrometry method (Figures 5d–f). As with the dye-binding method, the CSF of the one subject with elevated glycosaminoglycan levels demonstrated reduction; the others had low levels which remained low.

CSF white blood cell count was normal for most of the subjects (Figure 5b). There were intermittently high levels for two treatment subjects and two control subjects, but no study procedures were altered for the mild pleocytosis. CSF protein was high for most of the subjects (Figure 5c), likely reflecting altered CSF physiology. One subject had severely high CSF protein, in the thousands, likely the result of CSF blockage in the spine (Froin syndrome), and she required spinal cord decompression surgery during the study.

3.5 Brain MRI

Similar to the neuropsychological testing results, brain volumes as measured on MRI were stable throughout the study (Figure 6). Overall, white matter volumes were lower than expected for age at baseline and throughout the study (Figure 6a and b) [7]. Gray matter volumes were also lower than expected for age at baseline (Figure 6c and d), with the exception of the youngest subject (Subject 3, red diamond), who had normal gray matter

volume for age. Corpus callosum volumes (Figure 6e and f) appeared to increase for all subjects during the second year of the study. Total ventricular volumes were also stable during the study (Figure 6g and h). No subjects required ventricular shunting during the study. One of the subjects had had a ventricular-peritoneal shunt for many years prior to the study.

Diffusion tensor imaging was performed (Figure 7). Fractional anisotropy for the whole brain white matter (Fig 7a and 7b) generally remained stable throughout the study, although a control subject with the lowest values did see an improvement after treatment was given. Mean diffusivity for the whole brain white matter (Fig 7c and 7d) also remained stable throughout the study.

4. DISCUSSION

We studied intrathecal enzyme replacement in non-transplanted patients with attenuated mucopolysaccharidosis type I and cognitive impairment. Our subjects ranged from 12 to 50 years of age at baseline. Over a randomized one-year period, there was no significant change in neuropsychological outcomes in either the treatment or the control group. We had based our initial study size calculations on preliminary data showing a mean −2 point decline per year in memory and IQ scores in attenuated MPS I patients [8]. There are several possible reasons why we did not observe an expected cognitive decline in these subjects. The data set was limited, and cognitive ability is heterogeneous in attenuated MPS I patients, which is due, in part, to genotypic heterogeneity. Two to six year old attenuated MPS I patients have normal intelligence; between the ages of six to twenty-five years, 43% of patients have borderline or impaired IQ [7]. In our study, two of the four control subjects had normal IQ, and they qualified for the study based on impairment in a different neuropsychological domain. Patients with normal IQ have milder cognitive disease and may not have the expected cognitive decline that is seen in some patients by young adulthood. However, we did not see decline in the other two control subjects (who had impaired IQ at the start of the study). It may be that in these subjects, a longer study duration is needed to demonstrate cognitive decline.

We found no significant improvement on neuropsychological testing in treated subjects when compared to control subjects. While a lack of improvement is not unexpected, a possible factor is the relatively short time period of the study. In addition, while preclinical studies in dogs demonstrated robust uptake of laronidase into brain parenchyma with concomitant reduction in lysosomal storage, we do not know to what extent this occurs in humans. Antibodies to enzyme replacement may interfere with the effectiveness of treatment [21]. We did not find an association between the presence of anti-iduronidase antibodies and performance on neuropsychological testing. Genotypic and clinical heterogeneity in MPS I patients may also contribute to a difference in response to treatment.

In addition to the two subjects that required spinal cord decompression during the study, five of the six other subjects showed hyperreflexia in all extremities at baseline, probably representing asymptomatic spinal cord compression. Spinal stenosis in these patients was uniformly observed at the cervical level and this may have affected enzyme delivery to the

brain despite the fact that we screened all subjects for CSF flow obstruction at the start of the study with a nuclear medicine CSF flow study. All enrolled subjects had adequate flow from the lumbar cistern to the basal cisterns based on radionuclide detection at baseline. It is notable, however, that all subjects with elevated CSF glycosaminoglycan levels required spinal cord decompression surgery either before, during, or after the study. An additional subject who required spinal cord decompression surgery during the study never had CSF collected due to severe spinal dysostosis and possibly altered CSF physiology precluding collection during the procedure.

Other issues potentially affecting whether intrathecal enzyme can modify cognitive decline is age of onset of treatment and length of therapy. The median age of subjects in this study was 17.5 years, which may be too old to reverse whatever damage underlies cognitive decline.

Limitations of this study include the sample size and length of the control period. Although we had targeted an enrollment of sixteen subjects, we could only recruit eight. We hypothesize that attenuated MPS I patients and their families weighed the risk and pain of the relatively invasive intrathecal procedure versus the perceived stability of their cognitive status and decided not to participate in the study. Indeed, the stability of their cognitive status was also reflected in our study as no significant change in neuropsychological testing in the one-year control period. Furthermore, one year was an insufficient time period to distinguish between treatment and control groups; however, we faced an additional recruitment challenge with any control period longer than one year. Patient groups had expressed a disinclination to participate in a study with longer than a one-year control period and no access to potential treatment.

The study was also limited by logistical and technical challenges. Travel to the study site for an invasive procedure every three months was difficult, especially given the fact that many of the subjects had multiple other systemic medical issues. Access to the lumbar cistern was challenging due to spinal dysostosis in all subjects. Although initially about half of the subjects required fluoroscopic assistance to access the lumbar cistern, eventually all subjects had the procedure performed by a radiologist in the fluoroscopy suite. Dosing was limited by the total volume that can be administered at one time to a patient.

In summary, we did not find a significant effect on treatment with intrathecal Aldurazyme compared to control participants during twelve months of observation. There were many factors which could have influenced the outcome of this study. The short control period and no significant change in control subjects reduced the chance of distinguishing this group from the treatment group. The small sample size was due to difficulty recruiting patients. The treatment period was also relatively short and factors such as spinal cord stenosis may have interfered with delivery of enzyme to the brain. Most of the subjects have elected to continue onto an open-label five-year extension study. We are hopeful that a longer period of study will help elucidate many of these complex issues.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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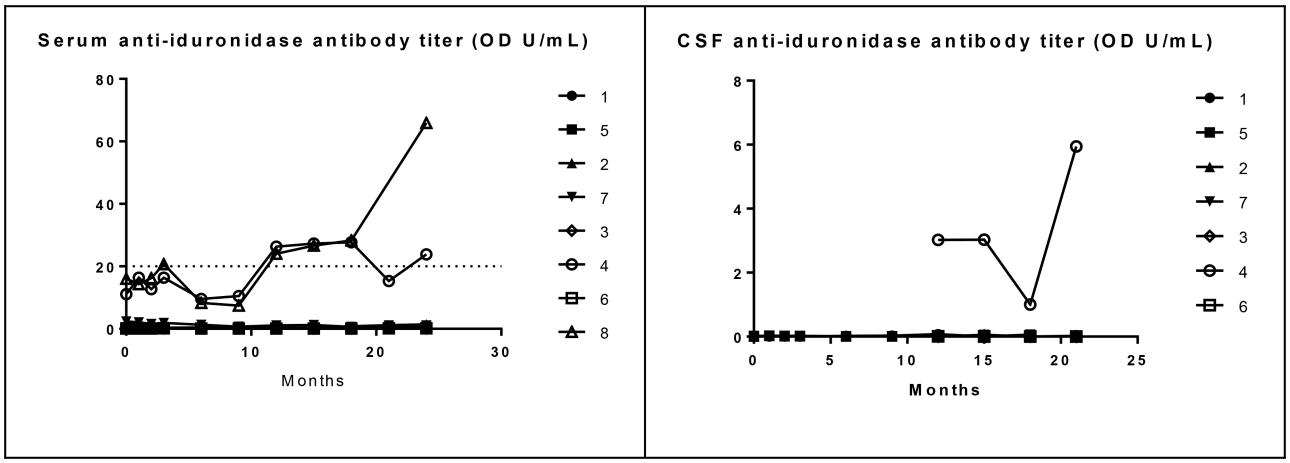


Fig 1. Anti-iduronidase antibodies

Anti-rhIDU antibody levels in MPS I subjects during the course of IT rhIDU treatments. Samples were drawn immediately prior to each IT rhIDU infusion. A dotted line at 20 OD U/mL represents what is considered a tolerant level of antibodies. Solid symbols represent subjects in the treatment group and open symbols represent subjects in the control group. One of the subjects, (Subject 8, open triangle) did not have CSF collected, so there is no CSF titer recorded.

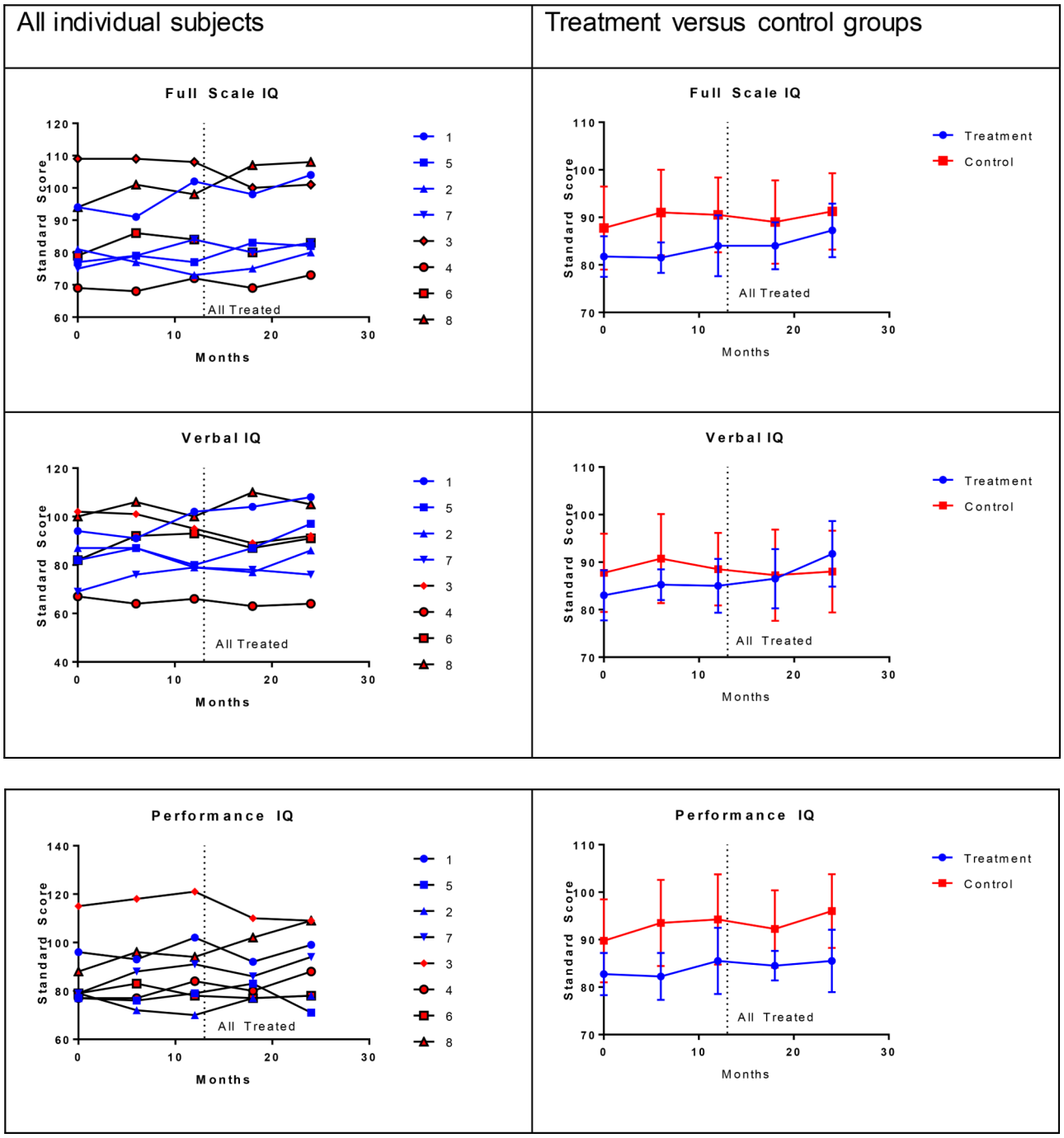
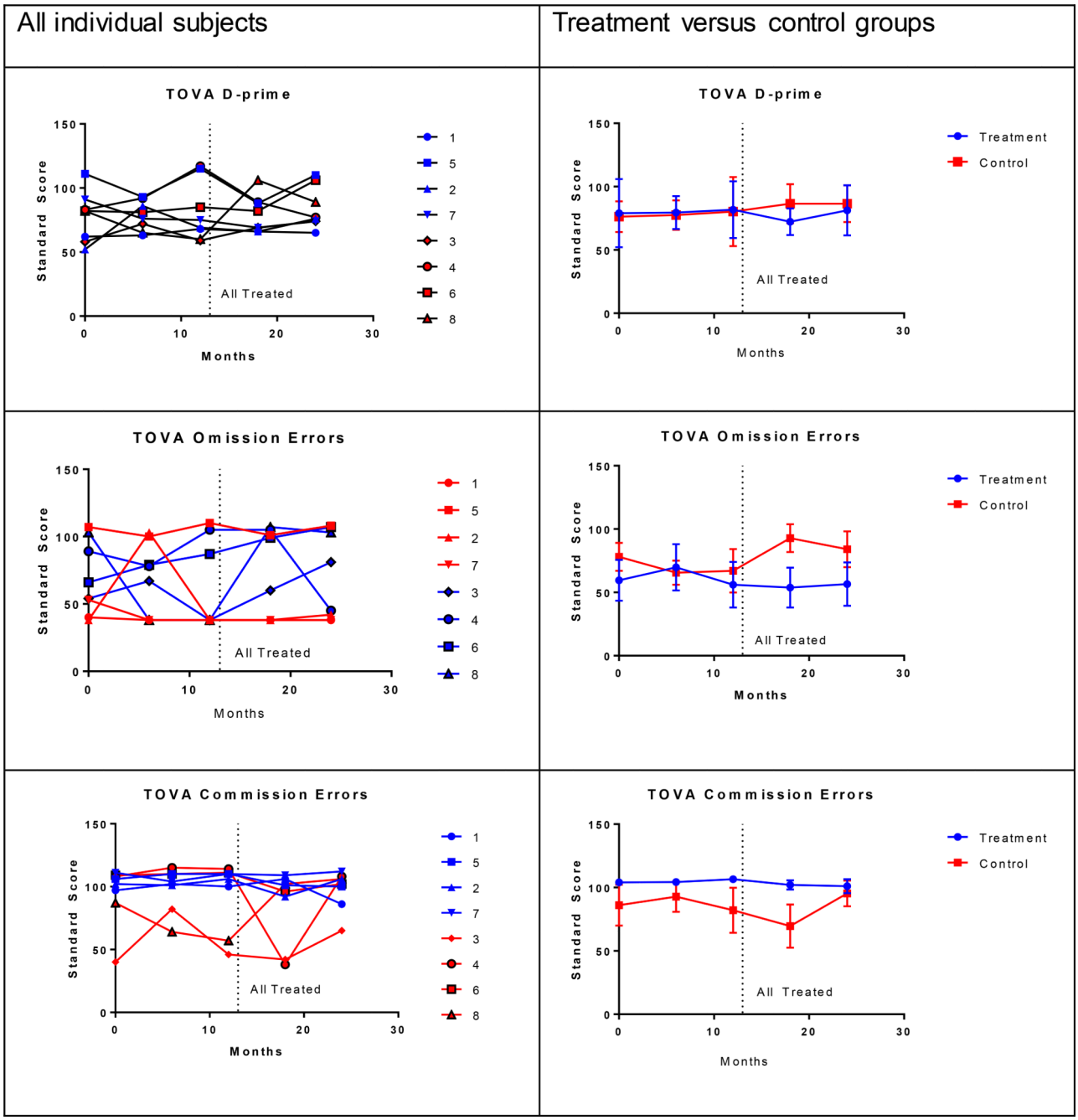


Fig 2. Wechsler Abbreviated Scale of Intelligence (WASI)

All standard scores for all eight subjects on the WASI are shown in the panels on the left. Testing was performed at Baseline (Month 0), 6, 12, 18, and 24 months. At the 12 month visit, all subjects received treatment after testing as indicated by the dotted vertical line. Group mean scores with standard errors are shown in the panels on the right. Blue symbols represent subjects in the treatment group and red symbols represent subjects in the control group.



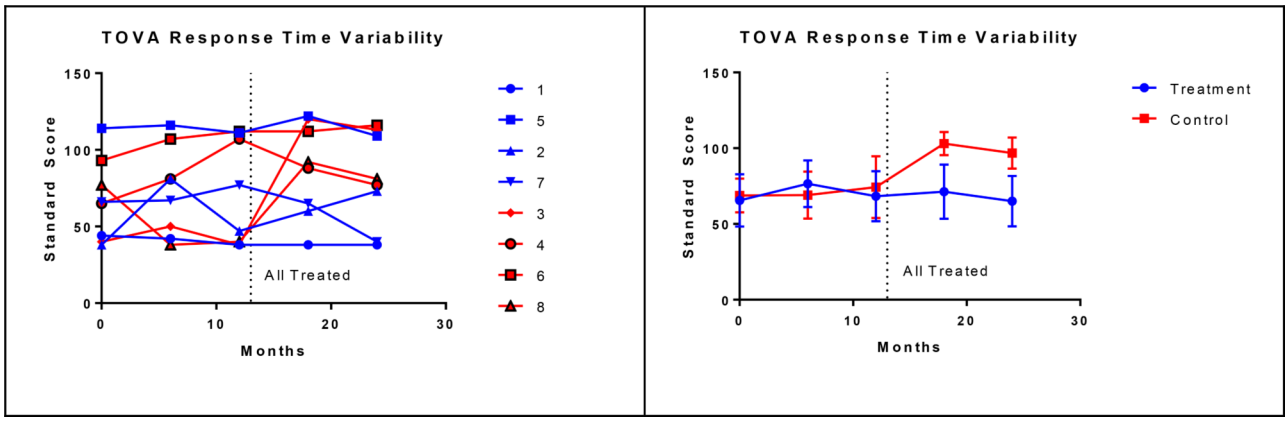


Fig 3. Test of Variables of Attention (TOVA)

All standard scores for all eight subjects on the TOVA are shown in the panels on the left. Testing was performed at Baseline (Month 0), 6, 12, 18, and 24 months. At the 12 month visit, all subjects received treatment after testing as indicated by the dotted vertical line. Group mean scores with standard errors are shown in the panels on the right. Blue symbols represent subjects in the treatment group and red symbols represent subjects in the control group.

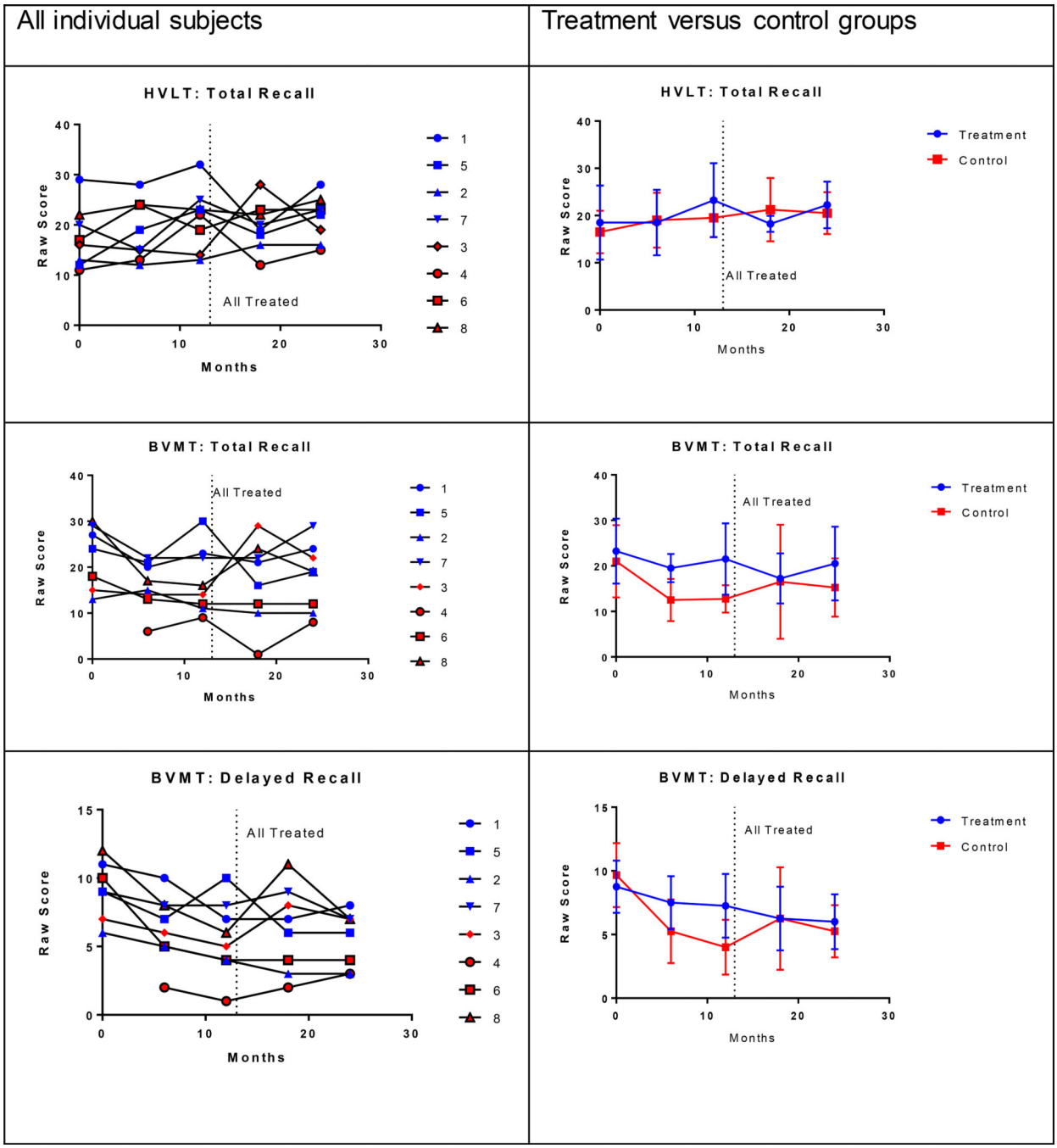


Fig 4. Hopkins Verbal Learning Test and Brief Visuospatial Memory Test

All raw scores for all eight subjects on the HVLT and BVMT are shown in the panels on the left. Standard scores are not shown because norms are not available for test subjects under the age of 16. Testing was performed at Baseline (Month 0), 6, 12, 18, and 24 months. At the 12 month visit, all subjects received treatment after testing as indicated by the dotted vertical line. Group mean scores with standard errors are shown in the panels on the right. Blue symbols represent subjects in the treatment group and red symbols represent subjects in the

control group. Subject 4, who was in the control group, was unable to perform the BVMT at the baseline visit.

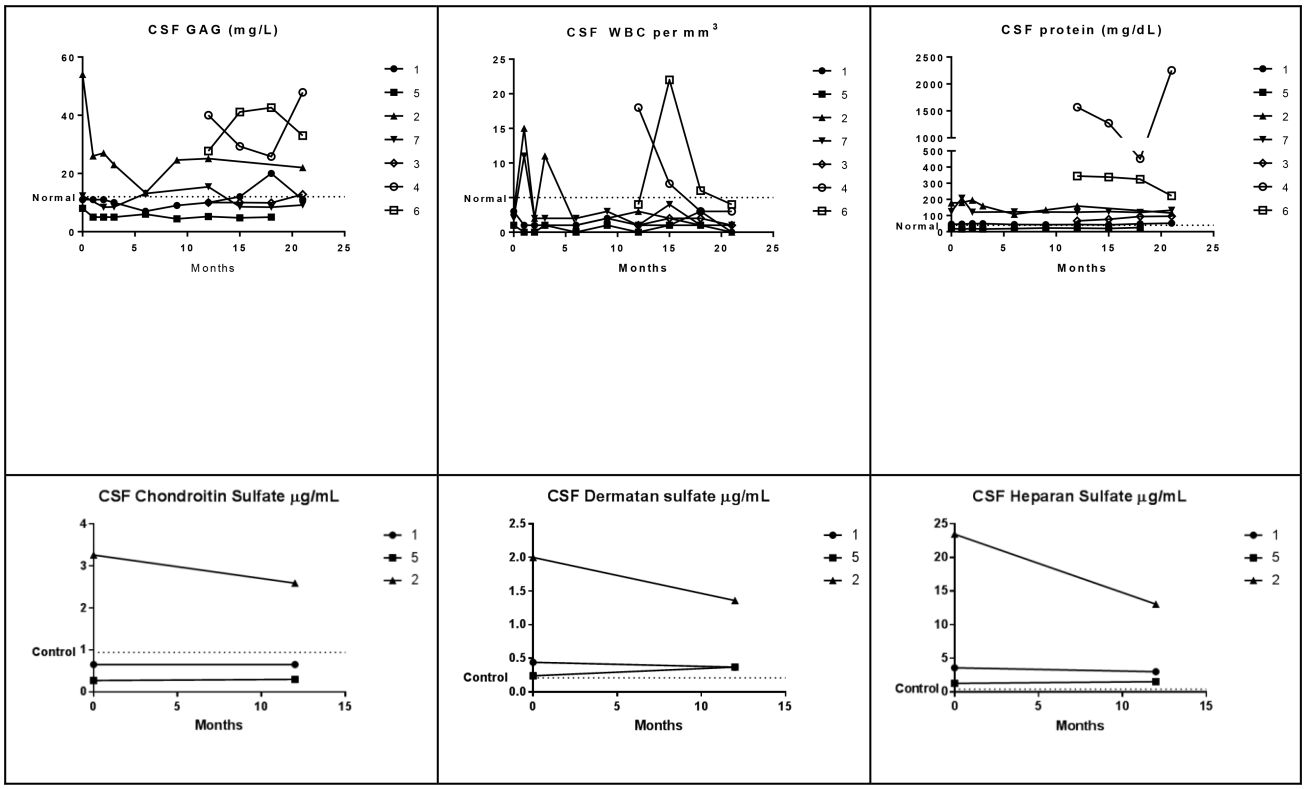
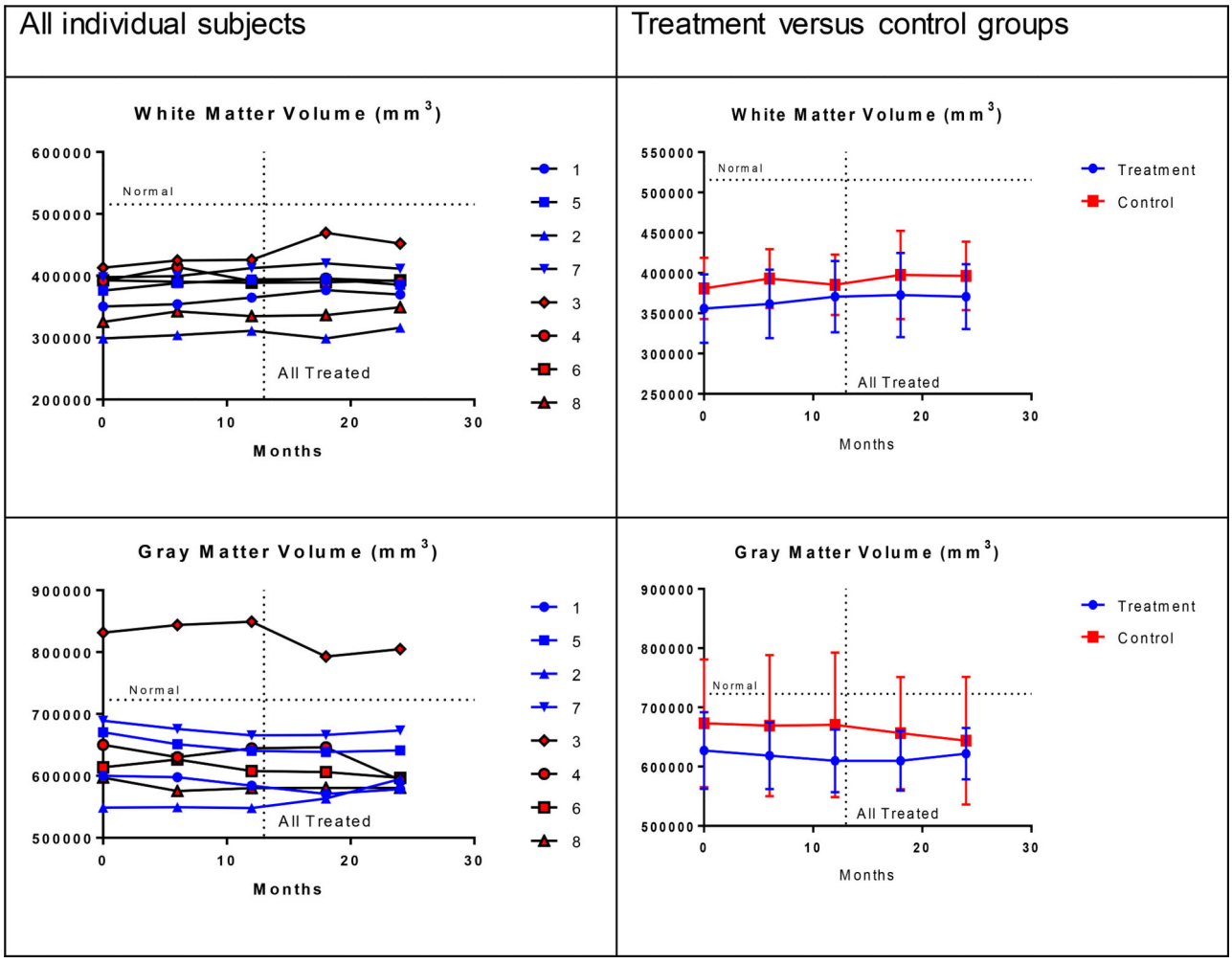


Fig 5. Cerebrospinal fluid glycosaminoglycans, leukocytes, total protein

Closed symbols represent treatment subjects and open symbols represent control subjects. 5a: Total glycosaminoglycans (GAG) by dimethylene blue dye assay. 5d-f: Heparan, chondroitin, and dermatan sulfate GAG by a UPLC-MS/MS method.



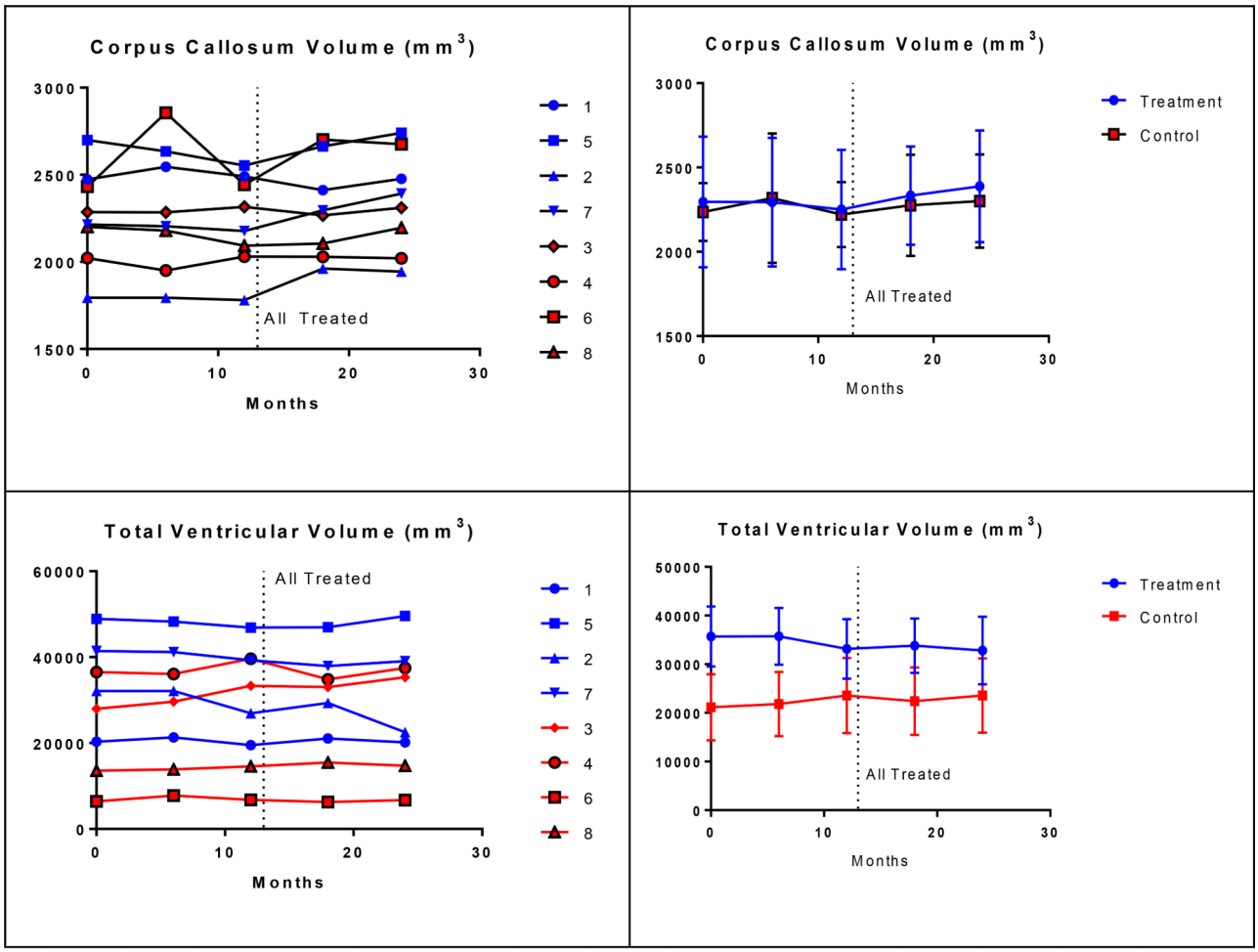


Fig 6. Brain MRI Volumetrics

All volume measurements for all eight subjects on the brain MRI are shown in the panels on the left. Testing was performed at Baseline (Month 0), 6, 12, 18, and 24 months. At the 12 month visit, all subjects received treatment after testing as indicated by the dotted vertical line. Group mean volumes with standard errors are shown in the panels on the right. Blue symbols represent subjects in the treatment group and red symbols represent subjects in the control group. The dotted horizontal line In Figures 6a-b represents mean volumes for a population of normal subjects who are 17–18 years of age, the median age for subjects in our study [20].

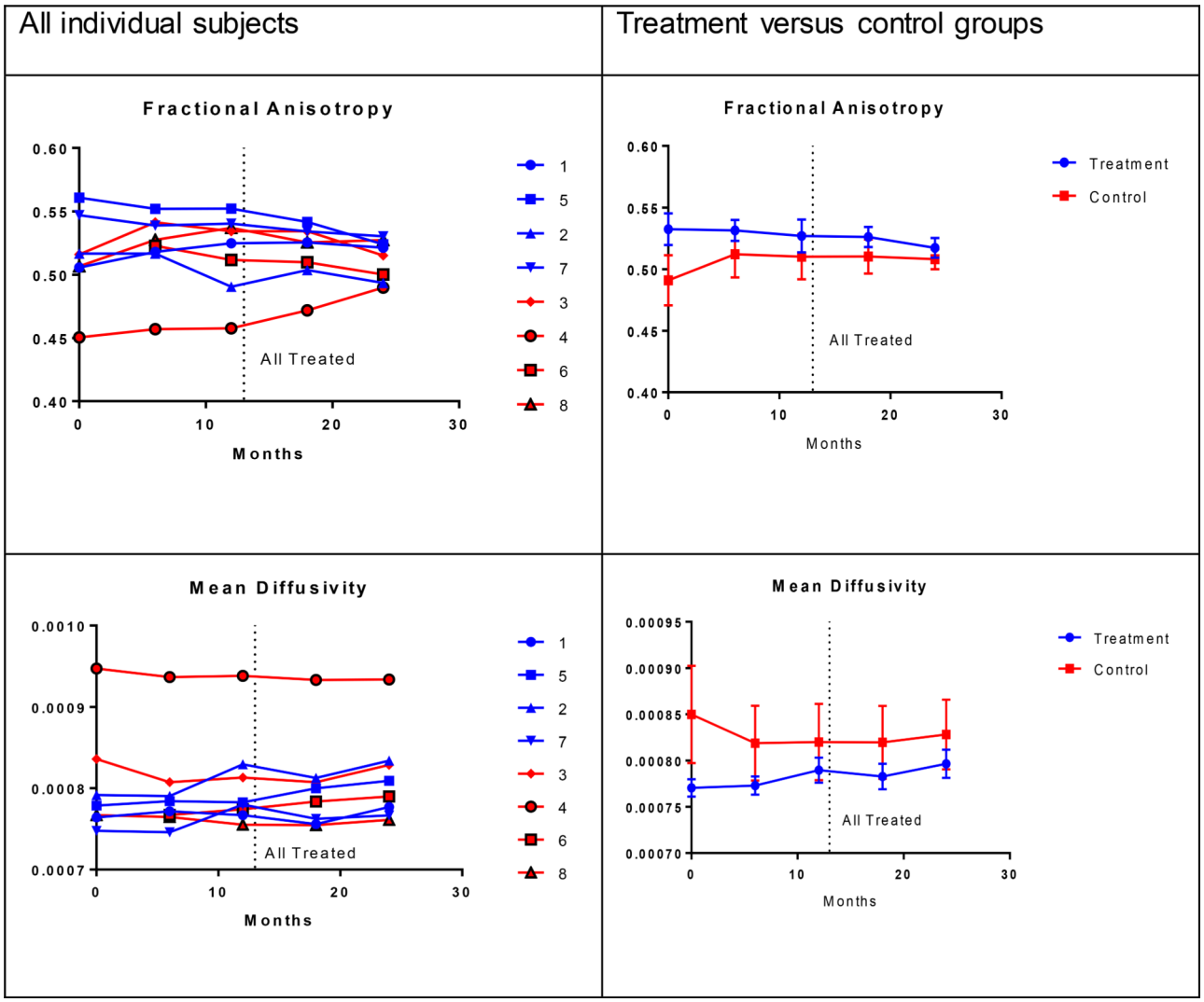


Fig 7. Whole Brain White Matter Diffusion Tensor Imaging

Whole brain white matter fractional anisotropy and mean diffusivity is shown for all eight subjects in the panels on the left. Testing was performed at Baseline (Month 0), 6, 12, 18, and 24 months. At the 12 month visit, all subjects received treatment after testing as indicated by the dotted vertical line. Group means with standard errors are shown in the panels on the right. Blue symbols represent subjects in the treatment group and red symbols represent subjects in the control group.

Table 1.

Schedule of study assessments and treatments

Month Number	Baseline	0	1	2	3	6	9	12	15	18	21	End Study (24)
Neuropsychological testing	X					X		X		X		X
MRI of brain	X					X		X		X		X
IT rhIDU: Control								X	X	X	X	
IT rhIDU: Treatment		X	X	X	X	X	X	X	X	X	X	

Table 2.

Baseline characteristics of study subjects

8 Subjects	4 Treatment Subjects	4 Control Subjects
Age at enrollment (years)	14–50	12–20
Median age (years)	18	17.5
Male (%)	3 (75%)	1 (25%)
MPS I genotypes	int3 425a>g, int5 1487g>a	65delC, H240R
	Q70X, Q380R	L238Q, 63delC
	Int3 -2a>g, L238Q	W402X, int11 -7c>t
	L238Q, W402X	L238Q, W402X
Baseline full scale IQ mean +/− sd	81.75 +/− 8.5	87.75 +/− 17.5

Table 3.

Serious adverse events and adverse events possibly related to treatment

Serious Adverse Events	**Relation to treatment**	**Number of subjects experiencing**	**Outcome**
Headache: hospitalization prolonged by one day	Possibly related	1	Resolved
Spinal cord compression	Not related	3	Surgical decompression for 2, monitoring for 1
Severe psychiatric symptoms	Not related	1	Ongoing treatment
Prostate cancer	Not related	1	Ongoing monitoring
Post-operative infection	Not related	1	Resolved
Vertebral dysostosis	Not related	1	Surgical fusion
Cardiac valvular disease causing heart failure	Not related	1	Ongoing treatment
Other adverse events			
Back pain	Possibly related	5	Resolved
Headache	Possibly related	4	Resolved
Groin pain	Possibly related	1	Resolved
Neck spasm	Possibly related	1	Resolved
Buttock pain	Possibly related	1	Resolved
Blurry vision	Possibly related	1	Resolved

Table 4.

Absolute change in Hopkins Verbal Learning Test Total Recall raw score (HTR) from baseline to months 12, 18, 24 adjusted for baseline HVLT total recall raw score with model-based standard errors.

Outcome	Control Group Mean (sd)	Treatment Group Mean (sd)	Adjusted Mean Difference Estimate [Trt-Ctrl] (95% CI)	P-value
Absolute Change in HTR from Baseline to Month 12	3.00 (5.60)	4.75 (4.65)	2.45 (−4.71,9.60)	0.533
Absolute Change in HTR from Baseline to Month 18	4.75 (5.50)	−0.25 (6.95)	−3.63 (−10.51,3.26)	0.349
Absolute Change in HTR from Baseline to Month 24	4.00 (1.41)	3.75 (4.57)	0.49 (−3.22,4.20)	0.805