



Toileting Abilities Survey as a surrogate outcome measure for cognitive function: Findings from neuronopathic mucopolysaccharidosis II patients treated with idursulfase and intrathecal idursulfase

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ABSTRACT

An outcome measure of toileting skills, the Toileting Abilities Survey or TAS, with sensitivity to detect change in a neurodegenerative disorder such as MPS II, was developed. The TAS was used in a research study of patients ($n = 86$) with the neuronopathic form of MPS II to measure treatment benefit of intrathecal idursulfase. Treatment with idursulfase and intrathecal idursulfase is associated with significantly higher individual and overall toileting skills versus treatment with idursulfase alone.

1. Introduction

Mucopolysaccharidosis type II (MPS II, OMIM 309900) is a rare, X-linked disorder of glycosaminoglycan metabolism that is caused by a deficiency in the lysosomal enzyme iduronate-2-sulfatase (EC 3.1.6.13). In affected patients, glycosaminoglycans accumulate in lysosomes of various tissues and organs and contribute to the pathophysiology of MPS II. [1] In general, the disease progression follows a neuronopathic or non-neuronopathic form. In the neuronopathic form, symptoms generally range across the somatic, neurocognitive, and neurobehavioral spectrums. [2] This study evaluates whether a new caregiver outcome measure assessing toileting abilities is a valid method to capture change associated with an experimental therapy, intrathecal idursulfase, in the neuronopathic MPS II population. [3,4]

In clinical trials for MPS II, endpoints are generally standard neurocognitive and adaptive measures. However, patient cooperation can be poor, normative floors are often higher than the functional level of many in the neuronopathic population, and the measures are not

validated in this population. Adaptive measures may be more appropriate because they can be administered more frequently, and they assess day-to-day functioning, impacting patients' and their family's daily lives.

Toileting implicates cognitive ability (recognizing a task needs to be done, planning to do it, and carrying it out), physical ability (completing the tasks), perception (sensory input regarding the necessity of a task and its completion), and behavioral control (aligning one's actions with one's cognitive understanding, intentions, and physical ability). Multiple studies have demonstrated the relationship between activities of daily living and cognitive status. [5,6] Although little research exists on the precise relationship between functional ability and cognition in children, in the elderly, cognitive status has been established as a predictor of functional ability [7], and impairment in activities of daily living has been shown as predictive of future dementia. [8] Toileting has been associated with an individual's cognitive abilities in stroke patients [9], nursing home residents [10,11], community-dwelling elderly [7], dementia patients. [8], and Alzheimer's disease patients [12].

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Therefore, a measure of independent toileting offers the potential to measure the impact of a CNS-targeted therapy.

2. Method

The USFDA advocates that clinical trials measure outcomes relevant to the real-world experience of patients and families. [13–15] Caregivers of patients with MPS II have identified toileting as such a skill. The authors interviewed caregivers of patients with MPS II, including those enrolled in studies of intrathecal idursulfase and those receiving standard therapy (i.e., intravenous enzyme replacement therapy with idursulfase), and reviewed discussions in multiple MPS II social media groups. Discussions referencing intrathecal idursulfase focused predominantly on toilet training, fully independent toileting, the use of “pull-ups,” training regimens in school, and rarely, continence products. With respect to patients not on intrathecal idursulfase, the discussions predominantly focused on diapers and continence products with some discussion on the possibility of toilet training in younger ages or trip-training, and also the futility of toilet training in neuronopathic patients.

Only three previous studies reported data specifically about toileting abilities in MPS II. Each study found that only a small minority of neuronopathic patients achieved bowel/bladder control [16–18], with the loss of toileting abilities [18] and the failure to bowel/bladder train as an early indicator of neuronopathic involvement [16]. This research and findings led the authors to consider whether a sensitive measure of toileting could detect change in connection with an experimental therapy, especially where change may only be the slowing of natural progression or stability of current skills.

The Toileting Abilities Survey (TAS) was designed based on the instrument used in the Fundamentals of Toileting Training Study (FTTS), a longitudinal study of 267 typically-developing children published in the journal Pediatrics. [19] The 27 questions to measure the overall acquisition of independent toileting in the FTTS represent a much greater number than measures previously used in MPS II studies (MPS-HAQ includes four questions, and VABS-III includes eight questions on toileting), thus offering the potential for greater sensitivity than current measures. In addition, the five-point Likert scale offered additional sensitivity over the three-point Likert scale used in the VABS measures or similar surveys. Based on a focus group consisting of MPS II caregivers, two questions were removed from the FTTS, two new questions were added, and 16 existing questions were revised. Data on demographics, diagnosis, disease form and symptoms, and the use of assistive devices and treatments were also collected. The TAS was administered to MPS II caregivers through the Hunter Syndrome International Patient Registry on the Backpack Health platform. [20]

The study assessed the Toileting Abilities Percentage (TAP), calculated as the percentage of the highest score possible across the survey (27 skills \times 5-points on the Likert scale, reflecting “always” does all skills independently = 135) as 100%, with the minimum (27 skills \times 1-point on the Likert scale, reflecting “never” does any of the skills independently = 27) as 0%. The study also assessed the mean on each of the individual 27 toileting abilities. The group treated with both idursulfase and intrathecal idursulfase (Treatment Group) was compared to those treated with idursulfase only (Control Group).

3. Results & discussion

There were 186 initial responses to the TAS with 59% ($n = 110$) describing their child as having the neuronopathic form of MPS II, 24% ($n = 45$) described their child as having the non-neuronopathic form, and 17% ($n = 31$) reported not knowing which form their child had. To compare the patients receiving both idursulfase and intrathecal idursulfase with those receiving idursulfase only, 100 were eliminated because they did not meet the inclusion criteria, resulting in 86 relevant patients in the neuronopathic population: 32 receiving both idursulfase and intrathecal idursulfase (treatment), and 54 receiving idursulfase

alone (control).

Neuronopathic patients receiving intrathecal idursulfase ($n = 32$) reflected a mean TAP of 61% independent toileting which, compared with neuronopathic patients receiving only idursulfase ($n = 54$) reporting a mean TAP of 22% independent toileting, is statistically significant with a p -value of <0.0001 using a two-sample t -test.

A linear regression model to control for age and time on idursulfase shows that neither are statistically significant predictors, and the test for treatment difference p -value <0.0001 . Therefore, the difference in overall toileting abilities of those neuronopathic MPS II patients receiving idursulfase and intrathecal idursulfase versus those receiving only idursulfase is statistically significant when controlling for age and time on idursulfase.

In each of the 27 individual toileting skills measured in the TAS, the mean of treated patients ($n = 32$) exceeded that of untreated patients ($n = 54$), rising to statistical significance ($p < .05$) in every individual skill. That statistical significance is maintained even when controlling for age and time on intravenous idursulfase. For patients who initiated intrathecal idursulfase at 6 years of age or older, the age after which cognitive abilities are expected to be in decline, the Older Treatment Group ($n = 7$) also exhibited higher individual toileting skills, with every skill reaching statistical significance when compared to a control group ($n = 14$) 2:1 matched for current age, age at intravenous idursulfase initiation, and time on intravenous idursulfase. See Fig. 1.

Caregiver-reported data, including form of disease and treatments, is a limitation in this study. There is also a lack of prior research on MPS II and toileting abilities specifically as this was the first study of its kind. Longitudinal studies using the TAS in a natural history and treatment context would be beneficial and are forthcoming. Further research with a goal of correlating the TAS to validated neurocognitive measures is also recommended.

4. Conclusion

A caregiver-reported outcome measure assessing an activity of daily living important to independent functioning, such as toileting abilities, could be an appropriate surrogate measure of cognitive function. Utilizing the TAS to measure treatment benefit of intrathecal idursulfase exhibited sensitivity within individual toileting skills, as well as overall, represented by the TAP. Treatment with idursulfase and intrathecal idursulfase is associated with significantly higher individual and overall toileting skills versus treatment with idursulfase alone. The significant difference in TAP between the treatment and control groups (61% versus

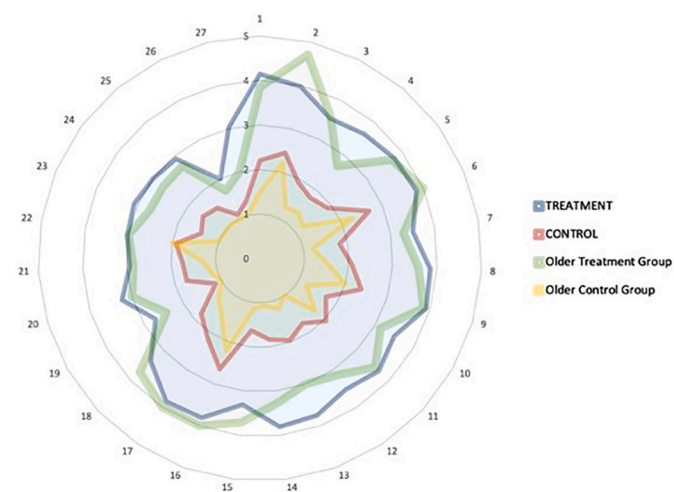


Fig. 1. Mean scores on the TAS (5-point Likert scale) for each of the 27 individual toileting abilities by treatment status and by intrathecal idursulfase initiation at 6 years of age or older matched to control.

22%) suggests that intrathecal idursulfase positively impacts the functions (cognitive and otherwise) necessary for toileting. Similar findings were found in patients who began treatment at age six or older.

Declaration of Competing Interest

MJH and KAS are caregivers to individuals with MPS II who participated in clinical studies of intrathecal idursulfase and thereby, received intrathecal idursulfase. MJH and KAS have received travel reimbursements and stipends from the sponsor of these studies, Takeda (formerly Shire) pursuant thereto. During the course of this research, both MJH and KAS have served terms as President and board members of Project Alive, the nonprofit funder of this research. Project Alive is pursuing a patent for the method of using the TAS to measure natural history and treatment benefit in MPS II and reports funds received from JCR Pharmaceuticals.

MJH reports consulting fees and advisory board honorarium from Denali Therapeutics and consulting fees from Seelos Therapeutics.

KAS reports consulting fees and reimbursements from REGENXBIO and reimbursements from Denali Therapeutics.

CJH is Chief Executive of FYMCA Medical Ltd and Chief Medical Officer of RareMD. FYMCA Medical Ltd engages with multiple pharmaceutical companies involved in the rare disease sphere but none related to this publication. CJH served as a Principal Investigator in the Phase I/II clinical study for intrathecal idursulfase.

KJB reports consulting fees from Denali Therapeutics, Seelos Therapeutics and REGENXBIO.

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