Safety and Efficacy of Rivastigmine in Adolescents with Down Syndrome: Long-Term Follow-Up

James H. Heller, M.A., M.S., C.C.C.,¹ Gail A. Spiridigliozzi, Ph.D.,² Blythe G. Crissman, M.S., C.G.C.,³
Jane Anne McKillop, M.S., C.G.C.,³ Haru Yamamoto, B.A.,⁴ and Priya S. Kishnani, M.D.³

Abstract

Following the completion of a 20-week, open-label study of the safety and efficacy of liquid rivastigmine for adolescents with Down syndrome, 5 of the 10 adolescents in the clinical trial continued long-term rivastigmine therapy and 5 did not. After an average period of 38 months, all 10 subjects returned for a follow-up assessment to determine the safety and efficacy of long-term rivastigmine use. Rivastigmine was well tolerated and overall health appeared to be unaffected by long-term rivastigmine use. Performance change on cognitive and language measures administered at the termination of the open-label clinical trial was compared between the two groups. No between-group difference in median performance change across the long-term period was found, suggesting that the long-term use of rivastigmine does not improve cognitive and language performance. However, two subjects demonstrated remarkable improvement in adaptive function over the long-term period. Both subjects had received long-term rivastigmine therapy. The discussion addresses the challenge of assessing cognitive change in clinical trials using adolescents with Down syndrome as subjects and the use of group versus individual data to evaluate the relevance of medication effects.

Introduction

DOWN SYNDROME (DS) is the most common genetic condition associated with intellectual disability, occurring in 1 of 733 births (Canfield et al. 2006). Several studies have suggested that cholinesterase inhibitors (ChEIs), such as donepezil hydrochloride and rivastigmine tartrate, may be an effective treatment for cognitive dysfunction in individuals with DS (Johnson et al. 2003; Heller et al. 2004, 2006; Kishnani et al. 2009). Heller et al. (2006) reported the results of a 20-week, open-label study of the safety and efficacy of liquid rivastigmine for adolescents with DS, the first clinical trial of rivastigmine on specific cognitive domains in pediatric DS. Despite the small sample size (10 subjects), rivastigmine was generally well tolerated (16 total adverse events, all known side effects of ChEIs) and a significant improvement in adaptive function, attention, memory, and language was found. At study completion, the parents of five of the subjects established off-label rivastigmine therapy for their children through their local physician. Five families did not continue rivastigmine therapy. This is a report of the follow-up evaluation of these 10 subjects.

Purpose

The purpose of this study was to determine (a) if there were any safety issues that developed with long-term use of rivastigmine, and

(b) does long-term use of rivastigmine improve language and cognitive skills.

Methods

Design

This “natural study” resulted from the unplanned split of the subjects into two groups, that is, those individuals who sustained long-term treatment with rivastigmine (long-term group) and those individuals who terminated rivastigmine use at the completion of the open-label trial (short-term group). All subjects were consented and brought back to Duke University Medical Center for a single follow-up visit on average 38 months after their final open-label trial visit. The follow-up visit consisted of a health review, a medication safety check and the completion of the same battery of cognitive and language tests administered during the open-label trial. Because of the small number of subjects, all reported group data are median scores.

Subjects

There were four boys and one girl in both groups. At follow-up, the average age was 15 years 7 months for the long-term subjects and 15 years 10 months for the short-term subjects. Of the five long-term subjects, two received rivastigmine at a dose of 6 mg divided

Departments of ¹Surgery, ²Pediatrics and Psychiatry, and ³Pediatrics, Duke University Medical Center, Durham, North Carolina.

⁴School of Medicine, Wake Forest University, Winston-Salem, North Carolina.

This study was supported by grants from The Anna Michelle Merrills Foundation for Down Syndrome Research and from The National Center for Research Resources (Grant No. 5UL1RR024128002), National Institutes of Health and NIH Roadmap for Medical Research. The contents of this study are solely the responsibility of the authors and do not necessarily represent the official view of the National Center for Research Resources or NIH.

bid; one received a dose of 4.5 mg divided bid; one received a 3 mg dose divided bid; and one received a 1.5 mg single dose. All subjects received a dose of 4.5 mg divided bid during the open-label trial. One of the 10 subjects (short-term subject 2) did not tolerate the 4.5 mg dose and was reduced to 3.0 mg for most of the trial.

Measures

Health status/medication safety

Electrocardiograms, medical history, and blood test for liver function were completed at the conclusion of the open-label trial and at follow-up. In addition, common side effects of rivastigmine were reviewed with the parents to identify adverse events.

Efficacy

At follow-up, the subjects were retested on the following cognitive domains:

- Adaptive behavior (Vineland Adaptive Behavior Scales [VABS]) as measured by the sum of the Communication, Daily Living Skills and Socialization domain standard scores of the VABS, Interview Edition (Sparrow et al. 1984);
- Language as measured by the total language score and the expressive language score of the Clinical Evaluation of Language Fundamentals–Preschool (Wiig et al. 1992) and the total score from the Test of Verbal Expression and Reasoning (Heller et al. 2000);
- Attention as measured by the Attention Sustained A (for ages 2–3 years) and B (for ages 4–5 years) subtests of the Leiter International Performance Scale–Revised (Leiter-R) (Roid and Miller 1997);
- Memory as measured by the Narrative Memory and Immediate Memory for Names subtests of the NEPSY: A

Developmental Neuropsychological Assessment (Korkman et al. 1998).

As in the open-label trial, the language, attention, and memory performance changes were reported in terms of raw score change, and the adaptive behavior change was measured in terms of the change in the sum of the domain standard scores.

Results

Health status/medication safety

At follow-up, rivastigmine-related adverse events (AEs) were reported for two of the five subjects in the long-term group. Three families did not report any AEs. The AEs for the child on the 6.0 mg dose were increased crying and increased urination. The increase in urination was temporary and the increased crying resolved with the introduction of birth control pills. A child on the 4.5 mg dose exhibited a temporary increase in defiance while receiving rivastigmine. In addition, increased urination and difficulty with morning arousal were noted in association with the use of atomoxetine. Overall, all subjects appeared healthy. No change in electrocardiogram or liver function was found for any subject.

Efficacy

Median (range) raw score performance changes for each group across the open-label trial (baseline vs. final visit) and the long-term (trial final visit vs. follow-up visit) periods are presented in Table 1.

Group performance change during the open-label trial. As a group, the children provided with long-term rivastigmine therapy demonstrated greater improvements in all test domains than the children with short-term rivastigmine therapy during the open-label trial. Without feedback from the research team, the parents' decision to pursue long-term/continued rivas-

TABLE 1. PERFORMANCE CHANGE PER TREATMENT GROUP (MEDIAN [RANGE]) ON MEASURES OF ADAPTIVE BEHAVIOR, LANGUAGE, ATTENTION, AND MEMORY DURING THE OPEN-LABEL TRIAL AND THE LONG-TERM FOLLOW-UP PERIOD

Test	Group	Performance change during the open-label trial	Performance change during the long-term follow-up period
Adaptive behavior			
VABS composite	Long term	6 (0, 27)	−14 (−34, 46)
	Short term	1 (−3, 14)	−14 (−29, 4)
Language			
TOVER	Long term	8 (0, 18)	2 (−2, 8)
	Short term	2 (−1, 5)	4 (−2, 7)
CELF-P total score	Long term	11 (1, 15)	10 (−7, 19)
	Short term	2 (−3, 9)	14 (−3, 19)
CELF-P expressive	Long term	12 (3, 14)	7 (−2, 12)
	Short term	−1 (−4, 8)	9 (−5, 14)
Attention			
Leiter attention A	Long term	7 (0, 20)	2 (0, 17)
	Short term	5 (3, 8)	0 (−4, 18)
Leiter attention B	Long term	7 (0, 23)	−1 (−16, 8)
	Short term	3 (−1, 20)	−1 (−4, 11)
Memory			
NEPSY memory for names	Long term	6 (−1, 9)	−1 (−6, 1)
	Short term	3 (−1, 16)	−2 (−6, −1)
NEPSY narrative memory	Long term	6 (−1, 9)	−1 (−6, 1)
	Short term	3 (−1, 16)	−2 (−6, −1)

CELF-P = Clinical Evaluation of Language Fundamentals; TOVER = Test of Verbal Expression and Reasoning; VABS = Vineland Adaptive Behavior Scales; NEPSY = NEPSY: A Developmental Neuropsychological Assessment.

tigmine was associated with the level of cognitive/language improvement exhibited by their child during the open-label trial.

Group performance change during the long-term period. Despite the fact that the long-term group exhibited a larger performance gain during the open-label trial, this trend did not continue through the long-term period. These results suggest that there was no additional benefit to the long-term use of rivastigmine.

Discussion

On average, the long-term group was 3 months younger than the short-term group; the time between the last open-label visit and follow-up was 6 months less than the short-term group, and the long-term group had higher adaptive behavior, language, and attention (Leiter Attention B) scores at the start of the open-label trial. The Leiter Attention A scale and NEPSY memory scores of the two groups were essentially identical at the start of the open-label trial.

Based on the results, we arrive at the following conclusions:

- (a) No safety issues developed from the long-term use of rivastigmine. Rivastigmine was well tolerated over the long term at doses ranging from 1.5 to 6.0 mg bid. As noted in the open-label trial, the reported adverse events were minor, temporary, and associated with the introduction of the drug following the completion of the open-label trial. Overall health appeared to be unaffected by long-term rivastigmine use.
- (b) There was essentially no difference in median performance change across the long-term period for either group, suggesting that the long-term use of rivastigmine does not improve cognitive and language performance.

However, an analysis of individual subject performance change suggests that the efficacy conclusion may not be as simple as suggested by the group data. For example, the VABS-adaptive behavior score decreased over the long-term period for most (6/10 subjects), whereas the VABS-adaptive behavior scores of 4 subjects, 2 from each group, increased over the same time period. The VABS-adaptive behavior scores of the two short-term subjects each increased 4 points and the VABS-adaptive behavior scores of the two long-term subjects increased 24 and 46, respectively. The large change in score by the two long-term subjects suggests that at least these two subjects may have made important gains in adaptive function over the long-term period.

The challenge with these results and the results of all the measures utilized to assess cognitive change in children and adolescents with DS is to determine their relevance. Although traditional cognitive and language tests are often used in clinical trials, the standard scores from these tests (standardized on a typically developing population) often place the performance of children and adolescents with DS at the floor of the standardization scale. One way to circumvent this problem is to use the simple raw score for baseline and posttreatment to measure performance change. Although this is an effective strategy to measure change, it provides little insight into understanding the relative importance of the change. For example, in this study, the expressive language score of one subject increased 7 points (more than a 50% gain from a score of 12 at the start of the long-term period to 19 at the end of the long-term period). The expressive language score of a subject in the other group increased 5 points (from 41 to 46) over the same period. Which gain is more important? In this case, it could be argued that the 5-point gain is more important because it demonstrates the

acquisition of higher-level concepts than the concepts acquired in the 7-point gain. Given two groups equal in age and cognitive ability, the measure of raw score change in cognitive and language measures is a reasonable approach to compare performance change across two groups. However, the more these two groups differ in these important characteristics, the less relevant large between-group differences become.

In this study, the short-term group was slightly older than the long-term group and the baseline performance of the short-term group was generally lower than the long-term group. In light of these challenges to score interpretation, the VABS-adaptive behavior scores were converted to VABS adaptive behavior composite scores. VABS adaptive behavior composite scores are standardized scores and were derived from the sum of the three VABS domain standard scores. VABS adaptive behavior composite score change was calculated for all 10 subjects across the open-label trial and the long-term period (Table 2). In an effort to understand the relevance of 10 individual change scores, the magnitude of standard score change was compared with the VABS criteria for test-retest reliability. The VABS manual provides criterion values for four confidence intervals, 68%, 90%, 95%, and 99%, at different ages.

As Table 2 indicates, during the open-label trial, the change in standard score performance of two subjects (long-term subjects 3 and 5) exceeded the VABS criterion level. Both subjects increased their VABS adaptive behavior composite scores by 8 points. This change in the older boy's performance exceeded the VABS 90% confidence interval and the change in the younger boy's performance exceeded the VABS 95% confidence interval. Over the long-term period, significant performance change was noted in four subjects. The performance gains of two long-term subjects (7 and 14 points, respectively) exceeded the VABS 95% and 99% confidence intervals. Two subjects, one from each group, demonstrated remarkable performance declines (a loss of 9 for the long-term subject and a loss of 10 for the short-term subject). Both declines exceeded the VABS 95% confidence interval for test-retest equivalence.

TABLE 2. INDIVIDUAL SUBJECT VINELAND ADAPTIVE BEHAVIOR COMPOSITE SCORE CHANGE DURING THE OPEN-LABEL TRIAL AND THE LONG-TERM FOLLOW-UP PERIOD

<i>Group/subject</i>	<i>Years of age at follow-up</i>	<i>Performance change during the open-label trial</i>	<i>Performance change during the long-term follow-up period</i>
Long term			
Subject 1	12	1	7 ^a
Subject 2	15	0	−4
Subject 3	16	8 ^b	−9 ^b
Subject 4	12	2	−4
Subject 5	15	8 ^a	14 ^c
Short term			
Subject 1	20	0	−3
Subject 2	15	1	−4
Subject 3	22	−1	2
Subject 4	15	4	2
Subject 5	14	0	−10 ^b

^aPerformance change exceeds 90% confidence interval for age.

^bPerformance change exceeds 95% confidence interval for age.

^cPerformance change exceeds 99% confidence interval for age.

In summary, only two subjects exhibited performance gains that exceeded VABS test-retest 90% confidence intervals during the open-label trial and during the long-term period. Both subjects were from the long-term group and one of the two exhibited significant gains during both periods. The long-term subject who exhibited significant gains during the open-trial demonstrated a significant loss in adaptive behavior skills during the long-term period. The loss of adaptive behavior skills occurred during the long-term period, a period of substantial family stress for this subject.

The results of the individual subject analysis in this study are concordant with other trials (e.g., Heller et al. 2004; Kishnani et al. 2009) that have reported that the effects of rivastigmine therapy are not consistent across individuals with DS, with many individuals showing little to no gains with therapy. This inconsistent pattern of performance across subjects suggests that there may be a subset of responders to cholinergic therapy within the larger group of adolescents with DS.

Addressing the question of drug efficacy in this study, we conclude that the group data fail to show cognitive or language improvement with treatment. However, of the two subjects who demonstrated significant gains in adaptive function, both received long-term rivastigmine treatment. The use of rivastigmine for these two individuals seems to be clinically relevant.

These apparently conflicting results raise important issues regarding the assessment of cognitive change in clinical trials (Harrison and Maruff 2008). For example, how do we measure the clinical relevance of ChEIs such as rivastigmine or other pharmacological interventions in this population? Is clinical relevance determined from group data or individual data? Cummings (2000) reported that when individuals with Alzheimer's disease are treated with cholinergic therapy, ~50% of the subjects show at least a 4-point gain on the Alzheimer's Disease Assessment Scale-Cognitive Portion, whereas ~30% of the subjects given placebo show at least a 4-point gain. In Alzheimer's disease, clinical relevance is defined by the additional 20% of the treatment group who reach the 4-point criterion performance level. Cummings added that the average response to cholinergic treatment in the Alzheimer's disease population includes a small group of subjects exhibiting striking improvement, matched by a proportionate group demonstrating uninterrupted decline.

The inconsistent pattern of response to cholinergic therapy in adolescents with DS suggests the possibility of genetic or epigenetic factors that could affect response to cholinergic therapy. Additional investigation may identify genetic modifiers that could influence outcome of individuals with DS (Blesa et al. 2006).

Disclosures

Mr. Heller has received grants and/or honoraria from Pfizer, Eisai, Roche, and Janssen. Dr. Spiridigliozzi has received honoraria from Pfizer, Roche, and Eisai. Dr. Kishnani has received grants and/or honoraria from Pfizer, Eisai, Roche, and Novartis. Blythe

Crissman, Jane Anne McKillop, and Haru Yamamoto have no conflicts of interest or financial ties to disclose.

References

- Blesa R, Bullock R, He Y, Bergman H, Gambina G, Meyer J, Rapatz G, Nagel J, Lane R: Effect of butyrylcholinesterase genotype on the response to rivastigmine or donepezil in younger patients with Alzheimer's disease. *Pharmacogenet Genomics* 16:771–774, 2006.
- Canfield MA, Honein MA, Yuskiv N, et al.: National estimates and race/ethnic-specific variation of selected birth defects in the United States, 1999–2001. *Birth Defects Res A Clin Mol Teratol* 76:747–756, 2006.
- Cummings JL: Cholinesterase inhibitors: Expanding applications. *Lancet* 356:1–4, 2000.
- Harrison J, Maruff P: Measuring the mind: Assessing cognitive change in clinical drug trials. *Expert Rev Clin Pharmacol* 1:471–473, 2008.
- Heller JH, Spiridigliozzi GA, Crissman BG, Sullivan JA, Eells RL, Li JS, Doraiswamy PM, Krishnan KR, Kishnani PS: Safety and efficacy of rivastigmine in adolescents with Down syndrome: A preliminary 20-week, open-label study. *JCAP* 16:755–765, 2006.
- Heller JH, Spiridigliozzi GA, Doraiswamy PM, Sullivan JA, Crissman BG, Kishnani PS: Donepezil effects on language in children with Down syndrome: Results of the first 22-week pilot clinical trial. *Am J Med Genet* 130A:325–326, 2004.
- Heller JH, Spiridigliozzi GA, Kishnani PS: TOVER: Test of Verbal Expression and Reasoning. Durham, NC: Duke University Medical Center; 2000.
- Johnson N, Fahey C, Chicoine B, Chong G, Gitelman D: Effects of donepezil on cognitive functioning in Down syndrome. *Am J Ment Retard* 108:367–372, 2003.
- Kishnani PS, Sommer B, Handen B, et al.: The efficacy, safety, and tolerability of donepezil for the treatment of young adults with Down syndrome. *Am J Med Genet* 149:1641–1654, 2009.
- Korkman M, Kirk U, Kemp S: NEPSY: A Developmental Neuropsychological Assessment, Manual. San Antonio, TX: The Psychological Corporation; 1998.
- Roid GH, Miller LJ: Leiter International Performance Scale-Revised. Wood Dale, IL: Stoelting; 1997.
- Sparrow SS, Balla DA, Cicchetti DV: Vineland Adaptive Behavior Scales-Interview Edition (Survey Form). Circle Pines: American Guidance Service; 1984.
- Wiig E, Secord W, Semel E: Clinical Evaluation of Language Fundamentals-Preschool. San Antonio, TX: The Psychological Corporation; 1992.

Address correspondence to:
James H. Heller, M.A., M.S., C.C.C.
Box 103856
Duke University Medical Center
Durham, NC 27710
E-mail: hell001@mc.duke.edu