Pediatric Neurology 61 (2016) 51–57

Contents lists available at ScienceDirect

Pediatric Neurology

journal homepage: www.elsevier.com/locate/pnu

Original Article

Pharmacologic Treatment of Rett Syndrome With Glatiramer Acetate

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ABSTRACT

BACKGROUND: Rett syndrome (RTT) is a severe neurological disease that primarily affects females. The level of brain derived neurotropic factor (BDNF) expression directly correlates with the severity of RTT related symptoms. Because Glatiramer acetate (GA) stimulates secretion of BDNF in the brain, we conducted the study with the objective to assess its efficacy in improving gait velocity cognition, respiratory function, electroencephalographic findings, and quality of life in patients with RTT. **METHODS:** Phase two, open label, single center trial. Inclusion criteria: ambulatory girls with genetically confirmed RTT, 10 years or older. Pre- and post-treatment measures were compared using the non-parametric Wilcoxon signed rank sum test and paired t-tests. **RESULTS:** Ten patients were enrolled and completed the trial. Gait velocity improved significantly (improvement range 13%-95%, $p=0.03$ for both tests) and emerged as an especially valuable outcome measure with excellent test- retest reliability of the 2 trials within sessions (intraclass correlation coefficient=0.94). Memory, and the breath holding index also improved significantly ($p\leq0.03$). Epileptiform discharges decreased in all four patients who had them at baseline. There was a trend towards improved quality of life, which did not reach statistical significance. **CONCLUSIONS:** This prospective open-label trial provides important preliminary information related to the efficacy of GA in improving gait velocity in female patients with RTT who are 10 years or older. The results of this trial justify the need for larger scale controlled trials of GA as well as provide a template for assessing the efficacy of other interventions in RTT.

Keywords: Rett syndrome, glatiramer acetate, gait, clinical trial

Pediatr Neurol 2016; 61: 51-57

Introduction

Rett syndrome is a severe neurological disease that affects 1:10000 females. It is caused by loss-of-function mutations in the methyl-CpG-binding gene (*MeCP2*).[1] Patients with Rett syndrome are typically completely dependent,

Article History:
Received February 27, 2016; Accepted in final form May 20, 2016
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http://dx.doi.org/10.1016/j.pediatrneurol.2016.05.010

nonverbal with no or minimal purposeful hand use, wheelchair bound, or with abnormal gait, with autonomic instability, seizures, and scoliosis.[2,3] Clinical diagnosis is based on a set of clinical criteria, the main of which include gait abnormalities, loss of acquired purposeful hand skills and spoken language, and stereotypic hand movements.[3]

MeCP2 acts as a transcription regulator of other genes.[1] One of the genes that have consistently shown expression changes when *MeCP2* is absent is brain-derived neurotrophic factor (*BDNF*), which functions as a key signaling molecule in brain development and plasticity.[4-6] The level of *BDNF* expression directly correlates with the severity of Rett syndrome–related symptoms. Overexpression of *BDNF* in affected mice led to a delayed onset of Rett syndrome–like symptoms, improved quality of life (QOL) and survival rates, and reversed electrophysiological deficits, whereas a decrease in the BDNF level led to earlier development of Rett syndrome–like symptoms and lethality.[7] Unfortunately, BDNF cannot be used in human trials of Rett syndrome because it does not cross the blood–brain barrier[8]; however, in animal studies, pharmacologic interventions that successfully stimulated BDNF (glutamatergic α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor activator—ampakine, tropomyosin receptor kinase B small molecule partial agonist, insulin-like growth factor 1 (IGF-1)—mecasermin, sphingosine-1-phosphate receptor 1 agonist—fingolimod) resulted in a marked functional improvement (locomotion, respiration, longevity) and treatment with IGF-1 had a positive effect on dendritic arborization, which is a histologic hallmark of Rett syndrome.[9-14]

Glatiramer acetate (GA) is a collection of synthetic polypeptides approved by the US Food and Drug Administration for the treatment of relapsing–remitting multiple sclerosis.[15] It activates GA-specific suppressor T cells in the periphery that cross the blood–brain barrier and stimulate secretion of several neurotrophic factors, including BDNF in the brain.[16-19] Administration of GA caused elevation of BDNF expression up to normal levels in several cortical areas in an animal model of Rett syndrome.[20] Incubation of neurons with GA for 24 hours resulted in about a twofold increase in neuronal expression of BDNF.[21]

In this open-label pilot study, we determined the effects of GA (Copaxone) administration in 10 girls with Rett syndrome. The primary end point was gait velocity because of its predictable course (highly unlikely to spontaneously improve), and relative stability compared to other Rett syndrome–related symptoms that can be assessed objectively but are characterized by significant hour-to-hour and day-to-day fluctuations.[3,22,23] Furthermore, it is noteworthy that gait velocity has been routinely used as an outcome measure in animal models of Rett syndrome[23] and in human studies of other neurological diseases because of its "excellent psychometric properties."[24-27]

Materials and Methods

Participants

In this phase 2, open-label trial, 10 girls with genetically confirmed Rett syndrome were recruited from the Rett Syndrome Center at Montefiore Medical Center (MMC), New York, United States. Six girls had epilepsy (well controlled in all). No changes were made to the patient medications during the study period. The study was approved by the Institutional Review Board of Montefiore Medical Center and Albert Einstein College of Medicine and registered at Clinicaltrials.org (NCT02153723). Written consent was obtained from all families. Inclusion criteria were: female patients with genetically confirmed Rett syndrome who were 10 years or older and ambulatory (without assistance at the time of their enrollment). Exclusion criteria included: prolonged QT syndrome, presence of comorbid non-Rett–related disease, presence of immunodeficiency requiring immunoglobulin therapy during the three months before enrollment, and allergy/sensitivity to GA, or mannitol (a contraindication as per the manufacturer).[15]

Assessments

Neurological evaluations, history updates and interviews with parents were performed by A.D. before drug initiation, before each drug escalation, and after the completion of the trial. Outcomes were assessed at baseline and after 24 weeks of treatment.

Treatment

The dose selected for treatment was 20 mg/day, which is the standard dose used and tolerated in this age group of children with multiple sclerosis.[28] Parents were trained to administer GA subcutaneously. The first dose was administered at the MMC Clinical Research Center; all subsequent doses were given by the parents, at home, according to the following dose escalating schedule: once a week for 4 weeks, twice a week for four weeks, and daily for the remaining 16 weeks of the trial. Total duration of treatment was 24 weeks. When any persistent intolerance (other than the mild transitory injection site redness) occurred, the dose was reduced to the previous maximally tolerated dose for the duration of the trial. To assess compliance of patients, a drug administration log was kept by parents and unused vials were returned. All patients were compliant, with no patient missing more than five doses during the 24-week trial (one patient missed five doses and another patient missed two doses during ongoing viral illnesses). Patients who showed improvements in gait velocity and whose parents were interested in continuing the treatment continued to receive daily treatment with GA as part of their medical care after the termination of the trial. These patients were followed clinically (A.D.) and underwent gait assessment about one year after the termination of the study.

Primary end point—gait velocity

Gait velocity (cm/second) was measured by a standardized walking test as used in previous studies by one of the coinvestigators (R.H.). Research assistants conducted quantitative gait evaluations, independent of the clinician's evaluation, using a computerized mat with embedded pressure sensors (GAITRite System). The walkway measures 8.5 × 0.9 × 0.01 m (L × W × H) with an active recording area of 6.1 × 0.61 m (L × W). Patients were asked to walk on the mat, at their normal walking speed, for two trials in a quiet and well-lit hallway. Start and stop points were marked by white lines on the floor and included 0.9 m (three feet) each for initial acceleration and terminal deceleration. Monitoring devices were not attached to the participants during the test. A parent walked alongside the electronic walkway to provide reassurance and, when indicated, support to maintain balance while walking. Software computed quantitative parameters based on footfalls recorded. Each trial was one walkway in length, and values analyzed were the mean of two trials computed automatically by the software.[25,27]

Secondary end points

Secondary end points included change in respiratory and cognitive functions, QOL, and electroencephalograph (EEG). Respiratory function monitoring was performed by evaluating ambulatory wake respirations over three hours with sleep monitoring equipment (Xltek, Natus Medical Incorporated, Oakville, ON, Canada) during the daytime at the