Neurologic features of Hutchinson-Gilford progeria syndrome after lonafarnib treatment

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ABSTRACT

Objectives: The objective of this study was to retrospectively evaluate neurologic status pre- and posttreatment with the oral farnesyltransferase inhibitor lonafarnib in children with Hutchinson-Gilford progeria syndrome (HGPS), a rare, fatal disorder of segmental premature aging that results in early death by myocardial infarction or stroke.

Methods: The primary outcome measure for intervention with lonafarnib was to assess increase over pretherapy in estimated annual rate of weight gain. In this study, neurologic signs and symptoms were compared pre- and posttreatment with lonafarnib.

Results: Twenty-six participants were treated for a minimum of 2 years. Frequency of clinical strokes, headaches, and seizures was reduced from pretreatment rates. Three patients with a history of frequent TIAs and average clinical stroke frequency of 1.75/year during the year before treatment experienced no new events during treatment. One patient with a history of stroke died due to large-vessel hemispheric stroke after 5 months on treatment. Headache prevalence and frequency were reduced. Four patients exhibited pretherapy seizures and no patients experienced recurrent or new-onset seizures.

Conclusions: This study provides preliminary evidence that lonafarnib therapy may improve neurologic status of children with HGPS. To address this question, we have incorporated prospective neuroimaging and neurologic assessments as measures in subsequent studies involving children with HGPS.

Classification of evidence: This study provides Class IV evidence that lonafarnib 115–150 mg/m² for 24 to 29 months reduces the prevalence of stroke and TIA and the prevalence and frequency of headache over the treatment period. *Neurology*® 2013;81:427–430

GLOSSARY

CI = confidence interval; FTI = farnesyltransferase inhibitor; HGPS = Hutchinson-Gilford progeria syndrome.

Hutchinson-Gilford progeria syndrome (HGPS) is a rare autosomal dominant disorder of premature aging for which there is no known cure, with an incidence of 1 in 4–8 million live births.¹ HGPS results from a mutation in *LMNA*, which causes accumulation of an aberrant form of the inner nuclear membrane protein lamin A, called progerin, resulting in cellular dysfunction.² Clinically affected children present with severe failure to thrive, accompanied by a phenotype characterized by alopecia, lipodystrophy, joint contractures, skeletal dysplasia, and atherosclerosis with preserved cognitive function.³ Children die of myocardial infarction or stroke at an average age of 13 years.⁴

Farnesyltransferase inhibitors (FTIs) are small molecules that reversibly bind to the farnesyltransferase CAAX binding site,⁵ leading to inhibition of progerin farnesylation, which is a crucial posttranslational processing step for protein intercalation into the inner nuclear membrane. In vitro treatment of progerin-containing cells with FTIs normalizes both structure and function.⁶ In addition, use of FTIs in the murine transgenic model of HGPS results in improved cardiovascular disease⁷ and extended lifespan.⁸ In a phase II study of the FTI lonafarnib, primary

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Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

outcome success was predefined as a 50% increase over pretherapy estimated annual rate of weight gain or change from weight loss to statistically significant on-therapy weight gain.⁹ In this study, we retrospectively reviewed neurologic features at baseline and during treatment with the oral FTI lonafarnib.

METHODS We used a retrospective design to analyze neurologic outcomes after treatment with lonafarnib. The open-label study was proposed to provide Class IV evidence for improved neurologic status. Primary outcomes were change in headache, TIA, and stroke frequency.

Patient selection. Participants were 3 years of age and older with clinically and genetically confirmed classic HGPS. All patients were heterozygous for *LMNA* c.1824C>T, p.Gly608Gly.

Dosage and administration. Lonafarnib (Merck & Co., Inc., Whitehouse Station, NJ) was initiated at 115 mg/m² before increasing to 150 mg/m² if tolerated after a minimum of 4 months. Participants received oral lonafarnib either by capsule or liquid suspension twice daily for 24 to 29 months.

Data. Most pretrial clinical information was obtained from The Progeria Research Foundation Medical and Research Database with parental consent (Brown University Center for Gerontology and Healthcare Research). For some patients, additional pretherapy clinical information was provided directly from the referring physicians. At study entry, participant and parent were administered a semistructured interview that included general health, cardiovascular neurologic symptoms, and stroke history. This was repeated in person at each study visit every 4 months and at completion of the study. All patients underwent serial physical and neurologic examinations at each visit; only patients with known prior seizures, strokes, and/or TIAs were also assessed by a neurologist.

Statistics. Data summaries are primarily descriptive and presented using percentages and 90% exact binomial confidence intervals (CIs). The comparison of headache incidence at study entry and completion is based on the McNemar test.

Standard protocol approvals, registrations, and patient consents. The study was approved by the Investigational Review Board of Boston Children's Hospital. Written informed consent and assent was completed in the languages of origin for enrollment in an open-label, dose-adjusted, phase II clinical trial of the oral FTI SCH66336 (lonafarnib). The study is registered with Clinicaltrials.gov (NCT00916747).

RESULTS Patients. Twenty-six patients with classic HGPS from 16 countries were enrolled in this phase II clinical trial of lonafarnib. Twenty-six patients had baseline data, and 25 of the 26 completed at least 2 years of lonafarnib treatment. This cohort comprised 10% to 13% of the estimated world population and 75% of identified children with HGPS from The Progeria Research Foundation International Progeria Registry at the time of study initiation. This world prevalence estimate of 200–250 is based on longitudinal data over a 13-year period, where known prevalence in the United States has remained stable at 1 in 30 million, expanded to worldwide population because of the sporadic nature of HGPS, without sex or ethnic bias (http://www.progeriaresearch.org/patient_registry.html).

Baseline neurologic status. All patients were assessed for neurologic symptoms and stroke history at baseline (table). Prior neuroimaging was available for review in a subset of patients (n = 13); at baseline, 8 of 13 patients (62%; 90% CI 35%–83%) had neuroimaging evidence of prior infarction (figure 1). Only 4 patients (15%) reported clinical history of strokes with frequency of 1.75/year in the 12 months before study entry (range 1–3/year). Three of these patients also had a history of TIAs. The remaining 4 patients displaying infarction on imaging were considered to have prior clinically silent strokes. Overall, 4 study patients reported a history of seizures, 3 of whom also had a history of stroke. At trial entry, 15 of 26 patients (58%; 90% CI 40%–74%) were experiencing headaches, with an average frequency of 0.9/week. Headaches had a migraine quality. Photosensitivity was noted in the majority of patients, with or without headache.

Table Demographics and neurologic baseline and posttherapy characteristics of children with Hutchinson-Gilford progeria syndrome treated with lonafarnib

	Before treatment ^a	During treatment ^b
Demographic characteristics at study entry		
Mean age, y (range)	7.6 (3–16)	
Sex, M/F	10/16	
Neurologic features		
Prior MRI at study entry	13/26	N/A
Evidence of infarction by MRI at study entry	8/13	N/A
Clinically evident stroke	4/26	2/26 ^c
Average stroke frequency in patients with known strokes before treatment (n = 4)	1.75/y	0.25/y
TIA	3/4	0/4
Headaches	15/26	7/25
Headache frequency	0.9/wk	0.37/wk
Seizures	4/26	0/25
Antiplatelet/anticoagulant use	n = 17	n = 15
Aspirin alone	14	14
Aspirin + clopidogrel	1	0
Aspirin + clopidogrel + acetazolamide	1	0
Aspirin + ticlopidine + warfarin + cilostazol	1	0
Aspirin + ticlopidine + cilostazol	0	1

Abbreviation: N/A = not applicable.

^aFor pretherapy group, this datum refers to the 12 months before treatment.

^bFor all on-therapy data except stroke incidence, total cohort n = 25 because of death of one patient from stroke at month 5 of therapy.

^cOne stroke occurred in a patient with history of clinical stroke and one occurred in a previously unaffected subject.

Figure 1 Axial FLAIR MRI of a 10-year-old child with Hutchinson-Gilford progeria syndrome

(A) Scattered small white matter infarcts (arrows). (B) Progressive deep white matter infarcts (arrows) 9 months later, before trial entry. This child experienced no clinically evident TIAs or clinical strokes during 24 months of lonafarnib treatment. FLAIR = fluid-attenuated inversion recovery.

Pretrial medications. Seventeen of 26 participants (65%) were taking daily aspirin, with an average daily dose of 5.8 mg/kg. Three patients were taking more than one antiplatelet or anticoagulant agent or acetazolamide (table). Other relevant medications included cholesterol-lowering agents ($n = 6$) and recombinant human growth hormone ($n = 6$).

Changes in neurologic status after lonafarnib therapy. Participants were assessed for recurrent neurologic symptoms at each study visit and at trial completion (table). One child with a history of strokes died of a

stroke after 5 months in the study. None of the 3 other patients who had reported clinical strokes at trial entry experienced recurrent TIA or stroke during treatment. One patient with no known history of clinically evident stroke and no prior neuroimaging studies experienced acute hemiparesis accompanied by headache and increased fatigue. CT angiogram demonstrated dense calcification and stenosis of both cervical internal carotid arteries, and subsequent MRI demonstrated a subacute infarction in the left frontal region (figure 2). Stroke was presumed to have been contributed by baseline cerebrovascular disease in the setting of relative dehydration.

Nonstudy medications were managed by each patient's own local treating physician. Overall, concomitant use of secondary anticoagulant agents was decreased during the study intervention. Two patients discontinued use of clopidogrel and one patient discontinued use of warfarin because of improved clinical symptoms and lack of new strokes or TIAs, although all 3 children continued daily aspirin therapy. Two patients without prior stroke symptoms discontinued use of aspirin because of minor bleeding.

The number of patients reporting headaches decreased from 15 at study entry to 7 at the time of study completion; there were no new patients reporting headaches during the study (McNemar p value = 0.005). In addition, there was a concomitant decrease in overall headache frequency to an average of 0.37/week (41% of baseline frequency). No patient experienced recurrent or new onset of seizures during the study period.

DISCUSSION Twenty-five patients with HGPS received the FTI lonafarnib for a minimum of 2 years. Treatment was associated with weight gain success, as well as cardiovascular, skeletal, and audiology improvements with minimal side effects.⁹ Before treatment, more than half of the study participants had a history of headaches, 4 had a history of TIA or strokes, and 4 had a history of seizure. During lonafarnib treatment, the observed frequency of stroke was decreased, which may be of particular relevance to those children with known symptomatic cerebrovascular disease and frequent TIAs at study entry. Only 1 of 4 patients with known history of clinical stroke had a new stroke. Overall, both the prevalence and frequency of headaches were reduced.

Neurologic outcomes were not identified as primary or secondary outcomes in the parent study because the reported prevalence rates of clinical stroke, TIA, and seizure were unknown and presumed too low to utilize as statistically analyzable outcome measures of treatment efficacy. Our pilot data suggest that treatment with lonafarnib may alter the progression of one of the primary morbidities (cerebrovascular disease) in

Figure 2 Cervical arteriopathy and stroke

(A) Coronal maximum intensity projection image of the neck CT angiography demonstrates bilateral internal carotid artery calcification and stenosis (arrows). (B) Axial FLAIR MRI in the same child demonstrates infarct of the left superior frontal gyrus (arrow). FLAIR = fluid-attenuated inversion recovery.

this devastating condition within a relatively short period of time. In addition, because headaches had a high prevalence within the cohort and may represent a presenting symptom for strokes and TIAs in children, the statistically significant decrease in both headache prevalence and frequency over the treatment period is promising.

In a recent natural history study in children with HGPS, radiographic evidence of infarction was found in 60% of patients, of which half were likely clinically silent.¹⁰ In subsequent clinical trials, we are evaluating MRI and magnetic resonance angiography of the neck and circle of Willis at initial trial entry and completion in order to better assess baseline characteristics, effects on the cerebrovasculature, and impact on clinically evident and silent infarcts after treatment interventions.

AUTHOR CONTRIBUTIONS

Dr. Ullrich: study concept and design, acquisition of data, analysis and interpretation, preparation of manuscript, critical review of manuscript. Dr. Kieran: study concept and design, acquisition of data, analysis and interpretation, critical review of manuscript. Dr. Miller: acquisition of data, analysis and interpretation, critical review of manuscript. Dr. Gordon: study concept and design, analysis and interpretation, critical review of manuscript. Dr. Cho and Dr. Silvera: acquisition of data, critical review of manuscript. Ms. Giobbie-Hurder and Dr. Neuberger: study concept and design, analysis and interpretation, critical review of manuscript. Dr. Kleinman: study concept and design, acquisition of data, critical review of manuscript.

ACKNOWLEDGMENT

Most importantly, the authors are grateful to the children with progeria and their families for their participation in this study. The authors thank the Family Inn (Cambridge, MA) and Devon Nicole House (Boston, MA) for housing families; Susan Campbell, MS, Nancy Wolff-Jenssen, and Nancy Grossman for medical records coordination; Kyra Johnson, Kelly Littlefield, Kiera McKendrick, Angela Kraybill, and William Fletcher for coordinator services; administrative, nursing, and processing staff at the CHB Clinical and Translational Study Unit; David Bowling and Rocco Anzaldi, RPh, for their expert pharmacy assistance; Merck Research Labs/Schering-Plough Research Institute for providing lonafarnib; Susan Arbuck, MD, Emily Frank, MS, David Harris, PhD, Bhavna Kantesaria, MS, Paul Kirshmeier, PhD, Antoinette Lee, and Yali Zhu, MS, for assistance with lonafarnib; and Stephen Young, MD, and Loren Fong, PhD, for collaborations.

STUDY FUNDING

This project was funded by The Progeria Research Foundation (PRFCLIN2007-01), the Dana-Farber Cancer Institute Stop & Shop Pediatric Brain Tumor Program, the C.J. Buckley Fund, the Kyle Johnson Fund, by a National Center for Research Resources, NIH grant to the Children's Hospital Boston General Clinical Research Center (MO1-RR02172), and a grant from the National Center for Research Resources, NIH, to the Harvard Catalyst Clinical & Translational Science Center (Harvard Catalyst) (UL1 RR025758-01).

DISCLOSURE

N. Ullrich receives royalty payments from the University of Alabama Birmingham Research Foundation and from UpToDate. She provided legal consultation for O'Connor, O'Connor, Bresse, and First. She received institutional support for neurofibromatosis and brain tumor research. M. Kieran has served as a consultant for Novartis Pharmaceutical and Merck Pharmaceutical. He has clinical trial agreements with Novartis, Merck, AstraZeneca, Advantagene Inc., GlaxoSmithKline Pharmaceutical, and Celtic Pharmaceutical. D. Miller has served as a consultant to SynapDx Corp. and served on the scientific advisory board for Integragen, Inc. L. Gordon is the parent of a child with progeria who participated in the study. She is the volunteer Medical Director for The Progeria Research Foundation. Y. Cho has served on a medical advisory board for Novartis and has received honoraria for speaking at a Novartis-sponsored CME symposium. V. Silvera, A. Giobbie-Hurder, D. Neuberger, and M. Kleinman report no disclosures. Go to Neurology.org for full disclosures.

Received September 13, 2012. Accepted in final form April 2, 2013.

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