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Adherence to Study Medication and Visits: Data from the BABY HUG Trial

Courtney D. Thornburg, M.D., M.S.[1], **Zora R. Rogers, M.D.**[2], **Michael R. Jeng, M.D.**[3], **Sohail R. Rana, M.D.**[4], **Rathi V. Iyer, M.D.**[5], **Lane Faughnan, R.N., B.S.N., C.C.R.P.**[6], **Leann Hassen, M.P.H.**[7], **Jennifer Marshall, R.N., A.D.N., C.L.N.C.**[2], **Roy P. McDonald, M.P.H.**[8], **Winfred C. Wang, M.D.**[6], **Xiangke Huang, M.D.**[9], and **Renée C. Rees, Ph.D.**[9] **for the BABY HUG Investigators**

[1] Department of Pediatrics, Duke University Medical Center, Durham, NC

[2] Department of Pediatrics, UT Southwestern Medical Center, Dallas, TX

[3] Department of Pediatrics; Stanford University School of Medicine, Palo Alto, CA

[4] Department of Pediatrics, Howard University, Washington DC

[5] University of Mississippi Medical Center, Jackson, MS

[6] Department of Hematology, St. Jude Children's Research Hospital, Memphis, TN

[7] Aflac Cancer Center and Blood Disorders Service, Children's Healthcare of Atlanta, Atlanta, GA

[8] Department of Pediatrics; University of Alabama, Birmingham, AL

[9] Clinical Trials & Surveys, Corp., Baltimore, MD

Abstract

Background—Subject retention and adherence are essential to maintain the power and validity of the Pediatric Hydroxyurea Phase III Clinical Trial (BABY HUG). We designed a study to assess adherence with study medication administration and study visits and to evaluate socioeconomic factors (SES) that may influence these measurements of adherence. These data are important for assessing impact of adherence on BABY HUG trial outcome and defining impact of SES on adherence.

Methods—Each subject's median study medication (MedAd) and mean visit adherence (VAd) were evaluated. We examined associations of adherence with SES of participating families.

Results—MedAd data were available on 153 of the 191 subjects who started randomized study medication. MedAd was 101.7% of volume prescribed, with 88.9% of subjects taking at least 80% of doses. VAd data were available on 185 of the 191 subjects who started randomized study medication. VAd was 97.3%, with 82.2 % of subjects having no missed visits. During dose titration, subjects had on average 12.9% higher medication adherence than subjects who were on a stable dose and had less frequent study visits. MedAd and VAd were not significantly associated with SES.

Conclusion—Subjects in the BABY HUG trial have had excellent adherence. SES was not associated with adherence, suggesting that SES should not be used as a criterion for enrolment in

Corresponding author: Courtney Thornburg, MD MS, Duke University Medical Center Box 102382, thorn006@mc.duke.edu, Telephone: 919-684-3401, Telefax: 919-681-7950.

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The authors have no relevant conflict of interest related to this manuscript.

clinical trials. Additional efforts are needed to maintain medication adherence, particularly when the interval between scheduled visits increases. (ClinicalTrials.gov number, NCT00006400)

Keywords

non-adherence; anti-sickling agents; clinical trial; study retention

INTRODUCTION

Adherence to prescribed medications has been reported to be poor with many chronic illnesses. In individuals with sickle cell anemia (SCA), adherence to prescribed regimens of penicillin prophylaxis, iron chelation, and pain medication has been sub-optimal [1–3]. Adherence with open label hydroxyurea (HU) has been studied to a limited extent in children with SCA. Oliveri and Vichinsky reported 4% non-adherence in a small series of 17 patients starting HU using computerized pill bottles and the frequency of bottle opening [4]. In the HUG-KIDS phase I/II trial better adherence was associated with higher fetal hemoglobin response [5]. In a prospective non-randomized clinical study of 122 children treated with HU, 12% of subjects with an initially good response to therapy lost this response and HU was discontinued by the provider because of suspected non-adherence [6]. In a study of 225 children, 13% of children stopped HU due to treatment failure and 7.5% due to non-adherence; the authors suggested that the treatment failures may have been due to poor adherence rather than lack of efficacy [7]. Adherence with HU has not been studied in a pediatric randomized clinical trial.

Excellent subject retention and adherence in randomized clinical trials are essential to the power and the validity of any trial [8–10]. Prior studies have evaluated predictors of attrition and adherence with study procedures in pediatric clinical trials [8–15]. These studies included evaluation of socioeconomic status. For example, Driscoll et al. reported that pre-randomization screening of participants on both demographic and psychological variables could identify those at greatest risk for study withdrawal or poor study protocol adherence [12].

The Pediatric Hydroxyurea Phase III Clinical Trial (BABY HUG) is an NHLBI and NICHD sponsored multi-center, randomized, double-blinded placebo-controlled study of daily oral HU in children with SCA (HbSS and Sβ^0 thalassemia) beginning at 9–17 months of age; the primary endpoints are preservation of spleen and renal function. We report longitudinal adherence data from the ongoing BABY HUG randomized clinical trial. We hypothesized that higher education level of the primary caregiver and household income may be associated with better adherence with study visits and taking study medication. Therefore, we evaluated SES and other demographic factors that may influence adherence.

METHODS

Study Design

Subjects with HbSS or HbSbeta^{0}thalassemia were enrolled into the BABY HUG study between 9 and 17 months of age [16]. The trial began in October 2003 and will be completed in September 2009; the last patient was randomized to study treatment in September 2007.

One hundred ninety-three subjects were randomized, and 191 subjects began study medication. (Figure 1) Two patients were deemed ineligible. We analyzed data through April 24, 2008, providing at least six months of adherence data for each subject.

Study Visits

During the initial dose titration phase, randomized subjects were seen every two weeks after initiation of study medication to monitor adverse events and laboratory toxicities (e.g., low hemoglobin level, platelet count, absolute neutrophil count, or reticulocyte count; high serum creatinine, bilirubin, or alanine transferase). After eight consecutive weeks without hematologic toxicity, they were considered to be on a stable dose and the frequency of visits changed to every four weeks. If laboratory toxicity occurred a STOP order was conveyed to the Clinical Center and study treatment was halted. If toxicity resolved within two weeks, treatment resumed at the original dose; prolonged or recurrent toxicity resulted in decreasing the study treatment dose by 2.5 mg/kg once toxicity resolved. Once a stable tolerated dose was maintained for eight consecutive weeks, the length between follow-up visits was increased to four weeks. The total duration of study treatment for each subject was two years.

Study Medication Administration

At each study visit the prescription was sent to the Clinical Center's pharmacy. The pharmacist reconstituted the study medication, which was supplied in powder form, with 70 mL of sterile water and 40 mL of Simple Syrup to yield a concentration of 100 mg/mL. The sterile water and syrup were measured with a graduated cylinder or medication syringe. The majority of pharmacists recorded a final dispensed volume of 120 mL as indicated by the Manual of Operations (although actual volume was approximately 110 to 115 ml). Daily doses were measured and administered by the caretaker using either a 3 mL or 5 mL oral syringe. The pharmacist marked the subject's dosage on the syringe with either tape or a black mark. At each 4-week visit the patient was provided a new bottle with at least a 35 day supply of study medication.

Significant efforts were made throughout the trial by the study personnel at Clinical Centers to maintain adherence with study visits and study medication administration. Subjects received telephone calls one week prior to their study visits to remind them of the appointment. Assistance with transportation to the Clinical Center was given if requested. Investigators took into account the families' schedules and willingly evaluated subjects if they came late or on an unscheduled day. Real time feedback from the study pharmacists regarding the estimated remaining doses allowed the study coordinators to address missed doses with the family at each visit.

Adherence Measures

Both study medication adherence (MedAd) and study visit adherence (VAd) were examined. Subjects were included in the MedAd analysis if there were at least 10 occasions when a bottle was dispensed at a visit and returned at the next scheduled visit (with a non-zero volume), and no medication stop order occurred between the visits (Figure 1). The rationale for this approach was to have an adequate representation of medication adherence over the course of the study for each individual subject, to avoid including bottles that might have been spilled, and to avoid overestimating MedAd related to stop orders. MedAd was strictly monitored by measurement of the volume of liquid study medication returned at each clinic visit. The study coordinator collected the old study medication bottle and the pharmacist measured the remaining volume of study medication using a graduated cylinder, syringe or rarely a visual estimate based on bottle calibrations. Study medication adherence for each bottle was calculated as follows:

$$\frac{\text{amount consumed}}{\text{prescribed amount}} = \frac{(\text{amount dispensed}) - (\text{amount returned})}{(\text{daily dose prescribed}) \times (\#\,\text{days on dose})} \times 100\%$$

Each subject's MedAd was calculated using the median of the individual bottle measurements. The median was used to minimize the effect of bottles with more than 120% adherence which might suggest spilling or discarding the medication rather than consumption. A subject was defined as adherent in taking the study medication if his/her median MedAd was ≥80%.

Subjects were included in the VAd analysis if they had at least one visit at a stable dose (Figure 1). VAd was based on expected routine study visits. Study coordinators completed a missed visit form if a subject did not complete the scheduled routine visit within the defined window (scheduled date plus 1 week if in titration phase and plus 3 weeks when on monthly visits. Mean VAd % was calculated as follows:

$$\left[1 - \frac{\#\text{ of missed visit forms}}{\text{expected }\#\text{ of routine study visits}}\right] \times 100\%$$

SES Measure

Demographic data and SES data were collected upon enrolment in the study. These data included the employment status of the primary caregiver [full-time (≥35 hours per week), part-time (<35 hours per week), laid off, unemployed or currently looking for work, disabled, retired, keeping house, attending school ≥35 hours per week, attending school <35 hours per week, volunteer work, and other]; household income (reported in $10,000 increments from <$10,000 to ≥$150,000); number of adults in the household, number of other children in the household; and education level of the primary caregiver (≤4th grade, 5–8th grade, 9–11th grade, high school diploma, some college but no degree, associate degree in college, Bachelor's degree, Master's degree, professional school, doctorate). Due to sparse data (<20 subjects) in some of the SES strata, certain categories were collapsed for the analysis: employment status of the primary caregiver (full-time, part-time, student, unemployed); household income (<$20,000; $20,000–39,999; $40,000–79,999; ≥$80,000); number of adults in the household (1, 2, 3+); number of other children in the household (0,1, 2, 3+); and education level of the primary caregiver (below high school, high school, college, graduate school).

Statistical Analysis

Descriptive statistics including quartiles (Q1and Q3) were used to describe the subject population and adherence measures. Cochran-Armitage Chi square exact test for trend was used to determine associations between MedAd (adherent or non-adherent) and SES factors. Fisher's exact test was used for early withdrawal. Regression analysis with repeated measures was performed to examine the association between bottle adherence and time on study and frequency of visits. ANOVA was used to examine VAd among SES factor categories and MedAd. All analyses were undertaken using SAS version 8.2 (SAS Institute, Cary, NC).

RESULTS

Demographic data were available on 191 subjects who started study medication (Table I). One hundred fifty-three subjects were included in the MedAd analysis. The median MedAd was 101.7% (Q1= 93.2 %; Q3= 110.3%); 88.9% of subjects had MedAd of ≥80%. The mean VAd ± SD was 97.3% ± 8.4, with 82.2% of subjects having no missed visits. Only 13 subjects (7%) had VAd of <90%. Six of these 13 subjects eventually were withdrawn from the study because they were lost to follow-up. Early withdrawal from the study was not significantly associated with poor MedAd (Table II). However, during the dose titration

phase when subjects had visits scheduled every two weeks, subjects had, on average, a 12.9% higher MedAd than subjects who had scheduled visits every four weeks, regardless of time on study. Distribution of MedAd over time is shown in Figure 2. To date, no patients have been non-adherent with both study visits and medication administration. Three subjects had a calculated MedAd >150% for unclear reasons. Excluding these subjects from analysis yielded a median MedAd of 101.5% for remaining subjects (compared to 101.7% for all subjects).

SES Measures

All SES data were available for the majority of subjects (Table I). The only missing data were income records; 6/153 (3.9%) and 8/185 (4.3%) income records were missing for the MedAd and VAd analyses respectively. MedAd and VAd were not significantly associated with the education level of the primary caregiver, household income, the number of adults in the household, or other children in the household. The Clinical Center with the largest recruitment (University of Mississippi Medical Center) had a significantly higher proportion of families at the poverty level (<$20,000) (p=0.005) than other clinical sites, but was still able to recruit and retain patients for the study.

DISCUSSION

Achieving the primary objective of the BABY HUG study (to determine the effectiveness of HU in preventing loss of organ function) is dependent on adherence with study medication. Adherence assessments were built into the BABY HUG study protocol *a priori*. No subjects have been non-adherent with both study visits and medication administration. Only six subjects were withdrawn from the study due to poor VAd. The excellent overall adherence was at least in part due to extraordinary efforts by the study personnel to consistently reinforce the importance of adherence and to implement creative solutions to overcome barriers to participation in the trial.

There was a significant 12.9% lower MedAd during periods of less frequent study visits. Strunk et al. suggested that adherence is dynamic and may decrease over time, implying that during clinical trials investigators should continually reassess family circumstances that may limit study visit attendance and retention [10]. Our findings suggest that special efforts are needed to maintain MedAd, particularly when study visits become less frequent. Efforts should be made to prevent attrition and encourage continued participation by allowing the families to have flexible scheduling options within the clinic, recognizing warning signs such as conflicts between family members about study participation and intervening appropriately, and reminding parents of the implications that this study may have on the future treatment of SCA.

We had hypothesized that higher education level of the primary caregiver and household income would be associated with better adherence. We did not find this to be the case, suggesting that these commonly chosen SES indicators should not be used to prejudge the suitability of subjects for a RCT or limit the prescription of HU in clinical practice. However, there may have been a selection bias toward subjects who would have been expected to be more adherent with the study requirements because subjects who attended clinic regularly had more opportunity to be offered participation in the study. In addition, selection may have been biased toward adherent subjects by only including those who completed all the required pre-randomization studies.

Our study was limited by lack of a gold standard for measurement of adherence, particularly for liquid medication. Measurement of returned liquid medication, as in the BABY HUG trial, is more problematic than standard pill counts. Not only does the estimate depend on the

measurement accuracy of the amount dispensed and returned, but also the measurement accuracy of each dose dispensed by the parents. Spilled doses, either accidentally or due to difficulty in opening the safety cap and liquid lost on the outside of the syringe, will result in higher calculated adherence. In addition, most pharmacists dispensed the entire bottle of reconstituted study medication, and recorded 120 mL dispensed on the case report forms because the reconstitution instructions indicated a final expected volume of 120 mL. In general, pharmacists did not record the actual volume dispensed. Based on the amounts of liquids and study medication powder combined to make the study medication, the actual volume dispensed was usually 110–115 mL; this discrepancy would also yield a greater apparent adherence. Furthermore, the subjects may have taken an incorrect dose which would result in either a lower or higher calculated adherence. Inaccuracy with dosing of liquid medication is well described in the pediatric literature [17–19].

Despite these limitations, we made the best attempt to objectively measure medication adherence and captured these data consistently throughout the study. In comparison, many studies rely solely on parental or patient report and often there are no measures to document medication adherence. In one retrospective review, approximately 50% of clinical drug studies attempted to document medication adherence. The most common methods used to evaluate adherence with taking study medications were pill count (33%), self report (25%), drug assays (14%), direct supervision (9%), and electronic devices (5%) [20].

Accurate treatment adherence data are important for assessing the results of any clinical trial. Although differences in dose response are expected from pharmacokinetic and pharmacogenetic variability, adherence actually may be the most important predictor of response. In the BABY HUG study, overall study retention, MedAd and VAd have been excellent. We will continue to review adherence data as they accrue, but based on the current analyses we anticipate that the quality of the endpoint data will not be adversely affected by poor adherence. Education level of the primary caregiver and household income were not associated with better adherence, indicating that suggesting that SES should not be used as a criterion for enrollment in clinical trials. Our findings suggest that special efforts are needed to maintain medication adherence, particularly when study visits become less frequent.

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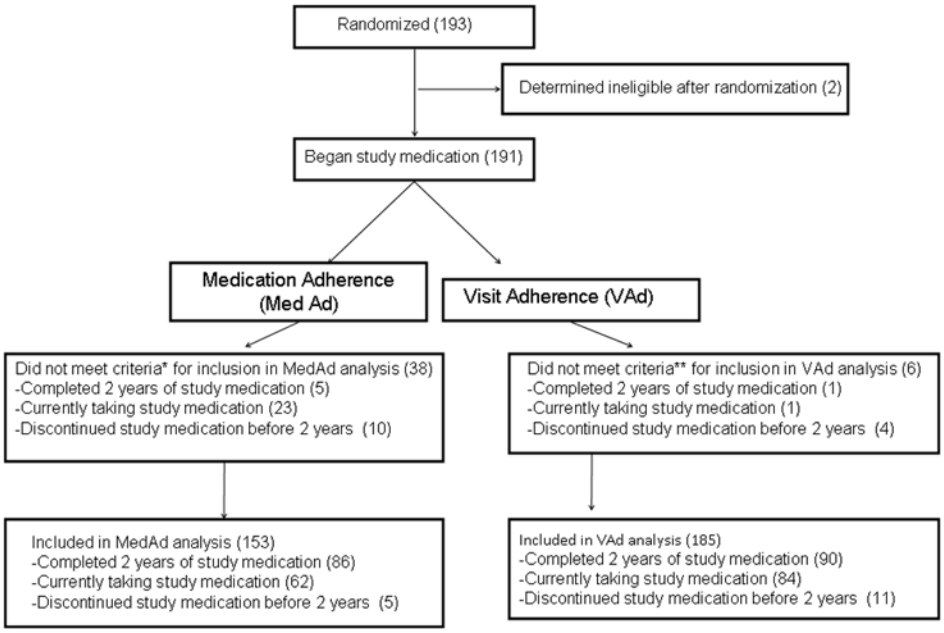

Figure 1. Flowchart of subjects included in the medication adherence and visit adherence analysis

The flowchart indicates which subjects were included in the MedAd and VAd analyses. Study status is indicated for subjects that were and were not included in each analysis. *Subjects were *not* included in MedAd analysis if they had <10 occasions when a bottle was dispensed at a visit, returned at the next scheduled visit (with a non-zero volume), and no medication stop order occurred between the visits. **Subjects were *not* included in VAd analysis if they had a genotype other than HbSS or when all study visits were at a non-stable dose.

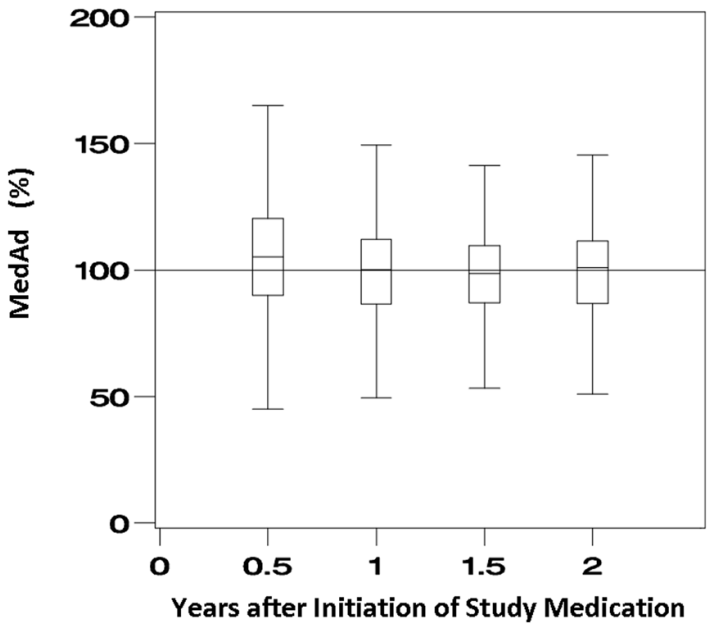

Figure 2. Study medication adherence over the course of the BABY HUG trial

The boxplots indicate the distribution of MedAd (%) at 0.5, 1, 1.5, and 2 years after the initiation of study medication. The horizontal line indicates 100% MedAd.

Table I

Characteristics of subjects receiving study medication in the BABY HUG trial.

	N	Mean (SD) / %
Age (yrs)	191	1.15 (0.23)
Gender	191	
Male	82	42.9%
Female	109	57.1%
Education of Primary Care Giver	191	
Below High School	30	15.7%
High School	50	26.2%
College	69	36.1%
Graduate School	42	22.0%
Income Level of Primary Care Giver	183	
<$20,000	75	41.0%
$20,000 – 39,999	45	24.6%
$40,000 – 79,999	44	24.0%
≥ 80,000	19	10.4%
Employment Status of Primary Care Giver	191	
Full time	98	51.3%
Part time	28	14.7%
Student	12	6.3%
Unemployed	53	27.8%
Number of Adults in the Household	191	
1	33	17.3%
2	110	57.6%
3+	48	25.1%
Number of Other Children in the Household	191	
0	40	20.9%
1	64	33.5%
2	44	23.0%
3+	43	22.5%

Table II

Reasons for early withdrawal in the BABY HUG trial.

Reasons for withdraw	Subjects not included in the MedAd analysis*	Subjects included in the MedAd analysis***
Inactive Follow-up Status**	6	0
Permanent Relocation to area with no BABY HUG Clinic	1	1
Withdrew consent	4	3
Placement on chronic transfusion program	1	0
Other reasons	0	1
Multiple reasons	1****	0
Total	11	5

* Subjects were *not* included in MedAd analysis if they had <10 occasions when a bottle was dispensed at a visit, returned at the next scheduled visit (with a non-zero volume), and no medication stop order occurred between the visits.

** Inactive follow-up status refers to ≥5 consecutive missed visits.

*** In the subjects included in the MedAd analysis, early withdrawal from the trial was not associated with MedAd.

**** Subject was inactive to follow-up and withdrew consent.