High-Dosage Ascorbic Acid Treatment in Charcot-Marie-Tooth Disease Type 1A
Results of a Randomized, Double-Masked, Controlled Trial

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**IMPORTANCE** No current medications improve neuropathy in subjects with Charcot-Marie-Tooth disease type 1A (CMT1A). Ascorbic acid (AA) treatment improved the neuropathy of a transgenic mouse model of CMT1A and is a potential therapy. A lower dosage (1.5 g/d) did not cause improvement in humans. It is unknown whether a higher dosage would prove more effective.

**OBJECTIVE** To determine whether 4-g/d AA improves the neuropathy of subjects with CMT1A.

**DESIGN** A futility design to determine whether AA was unable to reduce worsening on the CMT Neuropathy Score (CMTNS) by at least 50% over a 2-year period relative to a natural history control group.

**SETTING** Three referral centers with peripheral nerve clinics (Wayne State University, Johns Hopkins University, and University of Rochester).

**PARTICIPANTS** One hundred seventy-four subjects with CMT1A were assessed for eligibility; 48 did not meet eligibility criteria and 16 declined to participate. The remaining 110 subjects, aged 13 to 70 years, were randomly assigned in a double-masked fashion with 4:1 allocation to oral AA (87 subjects) or matching placebo (23 subjects). Sixty-nine subjects from the treatment group and 16 from the placebo group completed the study. Two subjects from the treatment group and 1 from the placebo group withdrew because of adverse effects.

**INTERVENTIONS** Oral AA (4 g/d) or matching placebo.

**MAIN OUTCOMES AND MEASURES** Change from baseline to year 2 in the CMTNS, a validated composite impairment score for CMT.

**RESULTS** The mean 2-year change in the CMTNS was −0.21 for the AA group and −0.92 for the placebo group, both better than natural history (+1.33). This was well below 50% reduction of CMTNS worsening from natural history, so futility could not be declared (P > .99).

**CONCLUSIONS AND RELEVANCE** Both treated patients and those receiving placebo performed better than natural history. It seems unlikely that our results support undertaking a larger trial of 4-g/d AA treatment in subjects with CMT1A.

**TRIAL REGISTRATION** clinicaltrials.gov Identifier: NCT00484510

Published online June 24, 2013.
Charcot-Marie-Tooth (CMT) disorders are inherited peripheral neuropathies and are among the most common genetic neurological disorders, with a prevalence of 1 in 2,400 individuals. Charcot-Marie-Tooth disease type 1A (CMT1A) is caused by a 1.4-megabase duplication on chromosome 17p11.2-3 and constitutes approximately 50% of all cases of CMT. The peripheral myelin protein 22 gene (PMP22; GenBank AC005703) is contained within the duplication, and the increased level of PMP22 causes the neuropathy.

High dosages of ascorbic acid (AA) reduced the messenger RNA (mRNA) levels of PMP22, improved function, and increased the numbers of myelinated peripheral nerve axons in the C22 mouse model of CMT1A. Subsequently, multiple clinical trials were undertaken to determine whether AA would slow progression or improve the neuropathy in subjects with CMT1A. Three randomized, placebo-controlled trials assessed patients for 1 year. A small Dutch study of 2-g/d AA and an Australian trial of 30-mg/kg/d AA in children showed no benefit in the primary end point of change in nerve conduction velocity. A French study of 179 adults noted no significant benefit of 1-g/d or 3-g/d AA over 1 year using the CMT Neuropathy Score (CMTNS); however, a benefit from 3 g/d was detected when the physiology component of the CMTNS was removed from the scoring. A trial conducted in Italy and the United Kingdom of 138 adults (aged 18-70 years) receiving 1.5-g/d AA compared with 133 adults receiving placebo for 2 years showed no effect of AA on the CMTNS.

We performed a clinical trial using high-dosage (4-g/d) AA for 2 years in subjects with CMT1A. We used the change in CMTNS as the primary outcome measure based on recommendations from the 136th European Neuromuscular Centre International Workshop on CMT that this was the best currently available primary end point for clinical trials. An AA dosage of 4 g/d was used because this was equivalent to the maximum amount ingested by mice and up to 10 g/d of AA has been well tolerated in humans. We used a futility design with a natural history control group.

Methods

Subjects
Subjects with CMT1A between the ages of 13 and 70 years were eligible for the study. Diagnosis of CMT1A was made by detecting the duplication on chromosome 17p11.2, performed by either pulsed-field gel electrophoresis or fluorescence in situ hybridization, or by the subject having a first- or second-degree relative with a documented duplication and having uniform motor conduction slowing of the median or ulnar nerve between 10 and 35 m/s. Written informed consent was provided by subjects aged 18 years or older and by parents or guardians for subjects younger than 18 years (with written assent from the subject). Subjects were excluded if they had criteria listed in eTable 1 in Supplement. The institutional review boards at all 3 participating sites approved the study (Wayne State University, Johns Hopkins University, and University of Rochester). We received an Investigational New Drug for the study from the US Food and Drug Administration (74970).

Randomization and Masking
Subjects were randomly assigned with 4:1 allocation to AA (80%) or placebo (20%). The AA was given as 4 g taken as four 500-mg capsules twice daily. Active drug and placebo capsules identical in appearance, taste, and smell were manufactured, packed, and labeled at a central pharmacy (CSP Clinical Research Pharmacy Coordinating Center, US Department of Veterans Affairs). The randomization plan was computer generated and included stratification by site and blocking to enhance preservation of the 4:1 allocation ratio at each site. Only a programmer in the Muscle Study Group Biostatistics Center and the investigational pharmacy had access to the treatment assignments during the trial.

Procedures
Potentially eligible subjects were evaluated at screening visits that included a history, confirmation of CMT1A genotyping, physical examination, recording of the CMTNS and Neuropathy Impairment Score (NIS), blood sampling for AA levels, complete blood count, electrolytes, blood urea nitrogen, creatinine, glycated hemoglobin, calcium, uric acid, and fasting blood glucose. Urinalysis and urinary pregnancy tests were obtained for women of childbearing age. Median or ulnar motor and antidiromic sensory nerve conduction studies were performed on the patient’s left side unless structural abnormalities necessitated use of the right side. A 36-Item Short Form Health Survey (SF-36) was obtained. If subjects met eligibility criteria, they were randomized and baseline skin biopsy specimens were obtained.

Follow-up visits were conducted at 6, 12, 18, and 24 months after baseline, at which time the physical examination, CMTNS, NIS, nerve conduction studies, SF-36, and serum AA levels were obtained. Drug compliance was measured by counting dispensed and returned pills and by serum AA levels. Adverse events were reviewed and vital signs obtained at each visit. The laboratory studies done at screening were repeated at 12 and 24 months and a second skin biopsy was performed at the 24-month (final) visit. Subjects and site investigators were then asked to provide guesses of the subjects’ treatment assignments.

Skin Biopsy and Real-Time Polymerase Chain Reaction Analysis
After informed consent was obtained, 2 adjacent 2-mm punch biopsy specimens were obtained as previously described. Biopsies were performed in the left volar forearm, 9 cm proximal to the ulnar crease at the wrist. Initial biopsies were performed 0.5 cm below a line connecting the ulnar crease at the wrist to the olecranon at the elbow, and final biopsies were performed 0.5 cm above the line. Real-time polymerase chain reaction was performed. The PMP22 mRNA levels were normalized to the 18S ribosomal band, S-100 protein mRNA (to normalize to Schwann cell number), and myelin basic protein mRNA (to normalize for myelin gene expression). Primers used in the reactions are listed in eTable 2 in Supplement.

Outcome Measures
The primary outcome measure was the change in CMTNS from baseline to year 2. Secondary outcome measures included 2-year changes in the CMT examination score, which was the CMTNS.
minus the 2 electrophysiological items,\textsuperscript{18} the NIS,\textsuperscript{14} ulnar motor nerve conduction velocity, nerve conduction distal latency, nerve conduction distal compound motor action potential amplitude, SF-36 summary and subscale scores, and PMP22 mRNA levels obtained from the skin biopsy specimens.

**Statistical Analysis**

To determine whether it would be prudent to test AA in a large confirmatory trial, we used a futility study design with a natural history control. A concurrent placebo group was included to facilitate double masking and to provide a descriptive check of the assumption that the natural history control group would yield changes in the CMTNS that were comparable to those of a concurrent placebo group.\textsuperscript{19}

The primary statistical analysis compared the mean 2-year worsening (increase) in the CMTNS in the AA group with a prespecified fixed value that represents a 50% reduction from the natural history of a mean increase in CMTNS of 1.33 points over 2 years;\textsuperscript{3} thus, a mean increase of 0.67 points on the CMTNS would represent a 50% reduction from expected. We formulated the statistical problem as that of testing $H_0: \mu \leq 0.67$ vs $H_1: \mu > 0.67$, where $\mu$ is the true mean worsening in CMTNS in the AA group. If $H_0$ were rejected, ie, if there were sufficient evidence that the mean worsening in the CMTNS from baseline to year 2 was not at least 50% less than that expected, it would be considered futile to pursue testing AA in a future confirmatory trial. This futility study approach to screening out ineffective agents has recently been used in other trials in neurodegenerative diseases.\textsuperscript{20–22}

The primary analysis estimated the adjusted mean changes in CMTNS in the AA and placebo groups using a mixed-model repeated-measures approach.\textsuperscript{3,4} The model included treatment group, month (6, 12, 18, and 24 months), treated as a categorical variable, the interaction between treatment group and month, site, and the baseline CMTNS as independent variables. The covariance matrix for the within-subjects measurements was specified as unstructured for model fitting. This approach appropriately accounts for missing data when estimating the model parameters under the “missing at random” assumption.\textsuperscript{24} This model was used to construct a t test to compare the mean increase in CMTNS in the AA group with the fixed value of 0.67 using a 1-tailed 10% significance level.

Data from the secondary outcome variables (CMT examination score, NIS, electrophysiological tests, SF-36 summary and subscale scores, vital signs, and laboratory test results) were analyzed using the mixed-model repeated-measures approach. Analysis of covariance was used to compare the treatment groups with respect to 2-year changes in log-transformed PMP22 mRNA levels, adjusting for center and the baseline level. Comparisons between the AA and placebo groups were chiefly descriptive owing to the small sample size of the placebo group. Adverse events were summarized as the percentage of subjects in each treatment group who experienced the event during the trial. We used $\chi^2$ tests to compare the AA and placebo groups with respect to the percentage of subjects thought (by subjects and by site investigators) to be receiving AA.

Data from our natural history study suggest that the standard deviation of the change in CMTNS from baseline to year 2 is approximately 2.2 points.\textsuperscript{39} A sample size of 80 subjects in the AA group was planned to provide 85% power to detect that the mean worsening in the CMTNS in the AA group was not at least 50% less than that expected, assuming that AA has no effect (ie, that the true mean decline is 1.33 points), using a 1-tailed t test and a significance level of 10%. If AA actually has no effect on the mean change in CMTNS, we had 85% power to detect futility of this agent. To account for a dropout rate of 20%, a sample size of 100 subjects was planned for the AA group.

**Results**

**Subject Characteristics**

One hundred ten subjects were recruited and evaluated between April 2007 and July 2011, with 87 patients receiving AA and 23 receiving placebo. Demographic and clinical characteristics were comparable between the treatment groups (Table 1). The mean (SD) age was 42.8 (14.7) years (range, 14-69 years), and 58% were female. The mean (SD) CMTNS at baseline was 16.5 (4.5), and the mean (SD) AA level was 0.87 (0.47) mg/dL (to convert to micromoles per liter, multiply by 56.78). Subjects in the natural history study (n = 72) had a slightly lower mean CMTNS and a higher mean NIS at baseline (Table 1).

**Subject Disposition**

Sixty-nine subjects (79%) in the AA group and 16 (70%) in the placebo group completed the study. Reasons for subject withdrawal are summarized in Figure 1. Two subjects in the AA group had the study drug temporarily suspended, one because of frequent muscle cramps and the other after an ankle fracture. Two others in the AA group had their dosage reduced, one to 3 g/d and the other to 2 g/d, owing to stomach upset.

**Primary Outcome Variable**

The adjusted mean change in the CMTNS over 2 years was $-0.21$ for the AA group and $-0.92$ for the placebo group; both performed better than the natural history group ($+1.33$) (Table 2 and Figure 2). The 90% lower confidence bound for the mean change in CMTNS in the AA group was $-0.63$, well below that representing a 50% reduction of CMTNS worsening from natural history ($+0.67$), so futility could not be formally declared ($P = .99$). The improvement in CMTNS in both treatment groups was apparent within the first 6 months and was sustained throughout the study (Figure 2). The results for the CMT examination score were similar to those of the CMTNS.

**Secondary Outcome Variables**

The results for the NIS were similar to those for the CMTNS, with the adjusted mean changes in the AA group ($+0.79$) and the placebo group ($-1.12$) both numerically less than that expected from natural history ($+2.73$).\textsuperscript{21} Results for other secondary outcome variables, including the SF-36 summary and subscale scores and the electrophysiological tests, are shown in Table 2. No treatment group differences were apparent, although the placebo group was small (n = 23).

The PMP22 mRNA levels were obtained at baseline and at 2 years in a subset of 69 subjects, 55 in the AA group and 14 in the
Notable group. No treatment effects were detected in these levels (Table 3). In agreement with previous reports,\(^7\) PMP22 mRNA levels were not associated with the CMTNS at baseline (\(r < 0.05\)) or with the CMTNS (\(r < 0.12\)) or AA level (\(r < 0.16\)) at 2 years.

Mean (SD) compliance with the assigned treatment (based on pill counting) was similar for subjects receiving AA (85.2% [23.0%]) and placebo (85.9% [19.6%]). Mean serum AA levels were significantly higher (\(P < .002\)) in subjects receiving AA than in those receiving placebo at all times after the baseline visit (Figure 3). Mean levels increased by approximately 1.0 mg/dL in the AA group and changed little in the placebo group. Forty-eight percent of subjects receiving AA and 33% of subjects receiving placebo thought they had been receiving AA (\(P = .24\)). Site investigators guessed that the subject was receiving AA for 76% of subjects in the AA group and 70% of subjects in the placebo group (\(P = .58\)).

**Safety**

Eighteen serious adverse events (AEs) occurred in 15 subjects (17%) in the AA group compared with 6 serious AEs in 5 subjects (22%) in the placebo group. The serious AEs are summarized in eTable 4 in Supplement. No serious AEs were judged to be related to the study drug.

The most common AEs were heartburn/gastrointestinal/vomiting/reflux, musculoskeletal, and upper respiratory tract infections (eTable 4 in Supplement). There were no significant differences at 24 months between the treatment groups with respect to changes in vital signs and laboratory test results, including urinary oxalate levels.

**Discussion**

This trial was designed to determine whether it would be futile to carry out a larger randomized, double-blind, placebo-controlled trial to examine the efficacy of high-dosage (4-g/d) AA in slowing the progression of CMT1A. Subjects had better outcomes than those reported in natural history studies. Thus, based on the prespecified primary analysis for this trial, high-dosage AA could not be declared futile for further study as a therapy for CMT1A. However, the concurrent placebo group, though small, had better than expected outcomes over a 2-year period. In addition, our results for both the AA and placebo groups were similar to results from the Italian/UK study in which the CMTNS was largely unchanged for both groups after 2 years (Figure 2). From all of the available
evidence, we conclude that it is unlikely that 4-g/d AA has a clinically meaningful effect on the course of CMT1A over a 2-year period. It is unlikely that the interpretation of our results was hindered by toxic effects from high dosages of AA as most patients tolerated the dosage well and there was little difference between the treatment groups in terms of AE. It is also unlikely that subject perception of whether they were receiving AA biased our results. The CMTNS is mainly investigator (examination) driven, and similar percentages of subjects were guessed by investigators to be receiving AA in the two treatment groups (76% and 70%). More than half of subjects in both groups thought they were receiving placebo.

Placebo Groups May Not Reflect Natural History
This clinical trial as well as the Italian/UK trial indicate that current natural history data for changes in the CMTNS over 2 years in CMT1A cannot be used in lieu of a placebo group in clinical trials. The factors accounting for the differences between our natural history data for the CMTNS and those from our placebo and active treatment groups in this trial are unclear. Systematic differences between current study participants and those in the natural history group may be partially responsible, although these groups had similar distributions of age, sex, and CMTNS (Table 1). It is also possible that the use of an allocation ratio of 4:1 (AA:placebo) had an influence on the relatively favorable outcomes in this trial given that both investigators and subjects were aware of this allocation ratio. Our findings are consistent with the positive placebo effect seen in therapeutic trials in diabetic neuropathy. An important question in this regard is whether the combined results of patients and placebo controls from both the Italian/UK and North American studies could be useful as a historical placebo cohort for future early-phase clinical trials in patients with CMT1A.

### Table 2. Outcome Variables by Treatment Group at Year 2

<table>
<thead>
<tr>
<th>Variable</th>
<th>Adjusted Mean Changea</th>
<th>Treatment Effect (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMTNS</td>
<td>-0.21</td>
<td>0.71 (−0.70 to 2.12)</td>
</tr>
<tr>
<td>CMTES</td>
<td>0.03</td>
<td>0.67 (−0.61 to 1.95)</td>
</tr>
<tr>
<td>NIS</td>
<td>0.79</td>
<td>1.91 (−2.24 to 6.07)</td>
</tr>
<tr>
<td>SF-36 score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MCS</td>
<td>-0.75</td>
<td>0.46 (−3.80 to 4.73)</td>
</tr>
<tr>
<td>PCS</td>
<td>0.01</td>
<td>0.39 (−2.99 to 3.77)</td>
</tr>
<tr>
<td>Physical functioning</td>
<td>-0.37</td>
<td>0.39 (−2.63 to 3.41)</td>
</tr>
<tr>
<td>Role-physical</td>
<td>0.01</td>
<td>1.56 (−2.69 to 5.82)</td>
</tr>
<tr>
<td>Bodily pain</td>
<td>0.17</td>
<td>−2.90 (−7.41 to 1.62)</td>
</tr>
<tr>
<td>General health</td>
<td>-0.71</td>
<td>2.82 (−0.42 to 6.05)</td>
</tr>
<tr>
<td>Vitality</td>
<td>-0.26</td>
<td>0.30 (−2.20 to 2.80)</td>
</tr>
<tr>
<td>Social functioning</td>
<td>-0.35</td>
<td>-0.15 (−5.16 to 4.86)</td>
</tr>
<tr>
<td>Role-emotional</td>
<td>-0.52</td>
<td>1.20 (−4.42 to 6.82)</td>
</tr>
<tr>
<td>Mental health</td>
<td>-0.86</td>
<td>-0.06 (−2.82 to 2.71)</td>
</tr>
<tr>
<td>Ulnar motor nerve</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CMAP amplitude, mV</td>
<td>0.04</td>
<td>0.07 (−0.81 to 0.95)</td>
</tr>
<tr>
<td>Distal motor latency, ms</td>
<td>-0.46</td>
<td>-0.12 (−0.87 to 0.64)</td>
</tr>
<tr>
<td>NCV, m/s</td>
<td>0.40</td>
<td>0.86 (−0.88 to 2.61)</td>
</tr>
</tbody>
</table>

Abbreviations: CMAP, compound motor action potential; CMTES, Charcot-Marie-Tooth examination score; CMTNS, Charcot-Marie-Tooth Neuropathy Score; MCS, mental component summary; NCV, nerve conduction velocity; NIS, Neuropathy Impairment Score; PCS, physical component summary; SF-36, 36-item Short Form Health Survey.

Figure 2. Changes in the Charcot-Marie-Tooth Neuropathy Score (CMTNS) Over the 2-Year Study

Adjusted mean changes in the CMTNS over 2 years are shown for the ascorbic acid group and placebo group. These are compared with the mean change at 2 years expected from published natural history and observed mean changes in the placebo groups in the French trial and the Italian/UK trial. Bars indicate 1 SEM. Larger (positive) changes indicate greater worsening.

### CMT1A Progression and Clinical Trials
Results from our trial as well as those of others emphasize the facts that CMT1A is a slowly progressive disease and that slowing of progression in adults may not be detectable within a 2-year period, particularly if mild improvement can occur from placebo effect alone. This, in fact, is consistent with a Dutch study that hypothesized that progression in adults with CMT1A might be more related to processes of natural aging than of disease progression itself. If CMT1A is relatively stable in adults,
Figure 3. Adjusted Mean Changes in Ascorbic Acid Levels Over the 2-Year Study

Mean changes in serum ascorbic acid levels are shown for subjects receiving 4-g/d ascorbic acid and those receiving placebo. Bars indicate 1SEM. Group differences in mean levels were statistically significant (P < .002) at all times. To convert ascorbic acid to micromoles per liter, multiply by 56.78.

Table 3. Log-Transformed Peripheral Myelin Protein 22 Messenger RNA Levels by Treatment Group

<table>
<thead>
<tr>
<th>Peripheral Myelin Protein 22 mRNA Level</th>
<th>Baseline</th>
<th>2-y Change*</th>
<th>Treatment Effect (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normalized to Ascorbic Acid</td>
<td>Placebo</td>
<td>Ascorbic Acid</td>
<td>Placebo</td>
</tr>
<tr>
<td>18S RNA band</td>
<td>~5.18</td>
<td>~4.79</td>
<td>0.22</td>
</tr>
<tr>
<td>S-100 protein mRNA</td>
<td>1.98</td>
<td>2.01</td>
<td>~0.02</td>
</tr>
<tr>
<td>MBP mRNA</td>
<td>5.20</td>
<td>5.28</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Table 3. Log-Transformed Peripheral Myelin Protein 22 Messenger RNA Levels by Treatment Group

Abbreviations: MBP, myelin basic protein; mRNA, messenger RNA.

* Values are adjusted mean changes from baseline to year 2, calculated from an analysis of covariance model that included treatment group, site, and the baseline value of the outcome variable as independent variables; see text for details.

then goals for future clinical trials will need to focus on detecting actual improvement in adult patients rather than just slowing disease progression. Alternatively, more sensitive outcome measures will need to be identified for future studies. Additionally, future studies may need to involve children, who were excluded from both the North American and Italian/UK studies. It is likely that much of the progression in CMT1A occurs during the first 2 decades of life. The recent publication of the CMT Pediatric Scale provides what will hopefully be a sensitive tool that is normalized for age to measure disability and progression in children with CMT1A. It may be that such a tool will permit the development of clinical trials in children with CMT1A.

State of the Field and Lessons Learned

Our trial provides an illustration of the potential dangers of using historical controls as the primary basis of comparison in a clinical trial. The problems may be accentuated when the historical controls are not derived from placebo groups of past, similarly designed clinical trials. In addition, when one uses a historical control group in a futility trial, it is helpful to include a concurrent placebo group but an allocation ratio as extreme as 4:1 (treatment-placebo) may not be wise; a ratio closer to 1:1 may be more appropriate to minimize potential placebo effects.

While it is disappointing that no dosage of AA has proven effective in treating CMT1A, we believe that it is important to not lose sight of what has been accomplished in just a few years because of these trials. Before the AA trials, there was no infrastructure in place to conduct large-scale multicenter trials for any form of CMT. To develop such an infrastructure, future investigators from the Italian/UK, French, Dutch, and North American trials met in Naarden, the Netherlands, to discuss the use of the CMTNS and other outcome measures in the AA trials. As the trials were nearing completion, these same investigators, along with those from Australia and elsewhere, met again in Naarden to discuss ways to improve the CMTNS, which subsequently led to the development of a newer version of the CMTNS and the CMT Pediatric Scale. It is because of the experience gained in the AA trials for CMT1A that the infrastructure is now in place to test new therapies in coordinated international trials.
High-Dosage Ascorbic Acid Treatment in CMT1A

Original Investigation Research


Conflict of Interest Disclosures: Dr Lewis has consulted for Baxter, CSL Behring, AlexCare, Novartis, and Bristol-Myers Squibb; Dr Shy has received grant support from the National Institute of Neurological Disorders and Stroke, Muscular Dystrophy Association, and Charcot-Marie-Tooth Association.

Funding/Support: This work was supported by the Muscular Dystrophy Association and the Charcot-Marie-Tooth Association. Wayne State University, the University of Rochester, and Johns Hopkins University were members of the Inherited Neuropathy Consortium of the Rare Disease Clinical Research Network supported by the National Institute of Neurological Disorders and Stroke and Office of Rare Diseases.

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Additional Information: The full trial protocol is available from Dr Shy (michael-shy@uiowa.edu).

Additional Contributions: We thank all the subjects who participated in the trial. Lisa Rowe, BA, worked in coordinating subject visits, Karen M. Krajewski, MS, helped in designing the protocol, Richard Kimball, RN, PhD, helped with subject recruitment and evaluations, and Arthur Watts, BS, helped with the statistical analysis.

REFERENCES