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Quinacrine treatment trial for sporadic Creutzfeldt-Jakob disease



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ABSTRACT

Objective: To determine whether oral quinacrine increases survival in sporadic Creutzfeldt-Jakob disease (sCJD).

Methods: This NIH/National Institute on Aging-funded, double-blinded, placebo-controlled, stratified randomization treatment trial was conducted at the University of California, San Francisco from February 2005 through May 2009 (ClinicalTrials.gov, NCT00183092). Subjects were randomized (50:50) to quinacrine (300 mg daily) or placebo with inpatient evaluations at baseline, and planned for months 2, 6, and 12. Subjects returning for their month-2 visit were offered open-label quinacrine. The primary outcome was survival from randomization to month 2.

Results: Of 425 patients referred, 69 subjects enrolled, 54 subjects were randomized to active drug or placebo, and 51 subjects with sCJD were included in survival analyses. Survival for the randomized portion of the trial (first 2 months) showed no significant difference between the 2 groups (log-rank statistic, $p = 0.43$; Cox proportional relative hazard = 1.43, quinacrine compared with placebo, 95% confidence interval = 0.58, 3.53). The quinacrine-treated group, however, declined less on 2 of 3 functional scales, the modified Rankin and Clinical Dementia Rating, than the placebo group during the first 2 months.

Conclusion: This interventional study provides Class I evidence that oral quinacrine at 300 mg per day does not improve 2-month survival of patients with sCJD, compared with placebo. Importantly, this study shows that double-blinded, placebo-controlled, randomized treatment trials are possible in prion disease. Furthermore, the quantitative data collected on the course of sCJD will be useful for future trials.

Classification of evidence: This study provides Class I evidence that quinacrine does not improve survival for people with sCJD when given orally at a dose of 300 mg per day for 2 months.

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GLOSSARY

AE = adverse effect; **CDR** = Clinical Dementia Rating; **CDR-SB** = Clinical Dementia Rating-Sum of Boxes; **CI** = confidence interval; **CJD** = Creutzfeldt-Jakob disease; **DSMB** = data safety monitoring board; **MMSE** = Mini-Mental State Examination; **NPDPS** = National Prion Disease Pathology Surveillance Center; **NPI** = Neuropsychiatric Inventory; **recHuPrP** = recombinant human PrP; **SAE** = serious adverse effect; **sCJD** = sporadic Creutzfeldt-Jakob disease; **UCSF** = University of California, San Francisco.

Sporadic Creutzfeldt-Jakob disease (sCJD), the most common form of human prion disease, is a rapidly progressive, uniformly fatal condition. Numerous drugs have been tried and have failed in animal models of prion disease.¹ Only one double-blinded, randomized controlled trial, with a primary outcome of cognitive function, has been conducted in sCJD; in that study, flupirtine showed mild benefits in cognition, but no survival benefit.² The antimalarial drug quinacrine and antipsychotic chlorpromazine were shown to eliminate prions *in vitro*,^{3,4} but chlorpromazine likely has a higher toxicity risk at the expected therapeutic dose compared with quinacrine.³ Because quinacrine was used safely for decades to treat cerebral malaria and is known to have excellent CNS penetration,⁵⁻⁸ we offered a compassionate quinacrine protocol to patients with sCJD referred to our center over 34 months. We found that those who chose quinacrine survived significantly longer

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Supplemental data at
www.neurology.org

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than those who did not choose quinacrine (see supplementary data on the *Neurology*[®] Web site at www.neurology.org). From this experience and case reports, we concluded that quinacrine was also well tolerated and easy to monitor in sCJD, with minimal toxicity.^{7,9} Encouraged by preliminary observations, we conducted a placebo-controlled, double-blinded treatment study to determine the efficacy of quinacrine on survival in CJD.

METHODS Standard protocol approvals, registrations, and patient consents. Study activities were reviewed and approved by our institutional review board and monitored by a data safety monitoring board (DSMB). Written informed consent was obtained from each subject or legally authorized representative. This study is registered at ClinicalTrials.gov, number NCT00183092.

Design. This study, funded by the NIH/National Institute on Aging, was a phase IIb, single-center, randomized, double-blinded, placebo-controlled study on the effect of oral quinacrine (300 mg per day) on survival in sCJD. The primary research question was: Is there Class I evidence that oral quinacrine at a dose of 300 mg per day for 2 months extends survival in sCJD? The study was conducted at the University of California, San Francisco (UCSF) between February 2005 and May 2009.

Subject selection. Inclusion and exclusion criteria are shown in table e-1. If eligibility of a subject was in question, at least 3 neurologists reviewed the case and made a consensus decision. Study recruitment and the detailed diagnostic process are discussed in the supplemental data.

Study drug initiation. Randomization to treatment group (placebo or quinacrine, 50:50) was performed by the pharmacist in variable block sizes (2, 4, and/or 6) and stratified by Barthel Index scores (≤ 30 or > 30) (see supplemental data for details on study drug assignment). After appropriate baseline laboratory safety testing (e-Methods), subjects received a loading dose of study drug: five 200-mg doses, administered orally every 6 hours and supplemented with 1 g of sodium bicarbonate to prevent gastrointestinal upset. After completing the loading dose, subjects began the study drug at 100 mg, 3 times daily. After monitoring for 24 hours, they were discharged home on study drug.

Study monitoring and safety. Telephone follow-up calls with caregivers occurred every 2 weeks for the first 2 months, during which study personnel collected modified Barthel Index,¹⁰ Rankin Scale,¹¹ Clinical Dementia Rating (CDR) scale,¹² and Neuropsychiatric Inventory (NPI) scores,¹³ and screened for quinacrine toxicity or side effects. Specimen collection kits (urine and blood) for safety monitoring were shipped to caregivers monthly, for remote safety monitoring (table e-2). Clinically significant adverse side effects, as judged by study physicians and the study pharmacist, resulted in a reduction or temporary discontinuation of study drug. All unexpected side effects, adverse effects (AEs), and serious AEs (SAEs) were reported to our institutional review board. The DSMB reviewed study safety and progress. A midstudy interim analysis was performed (see statistical analysis section and e-Methods).

Follow-up. Subjects were reevaluated and baseline testing was repeated at UCSF at months 2, 6, and 12 when possible. Subjects returning to UCSF for their month-2 visit were given the option of switching to open-label quinacrine (see e-Methods for

rationale). Subjects returning at month 2 who opted for open-label quinacrine were switched to oral quinacrine (at 100 mg, 3 times daily) without a loading dose and were monitored for 24 hours. Participants returning at month 2 could also choose to remain on study drug. Subjects not returning at month 2 stayed on the study drug.

After month 2, participants, including those who discontinued treatment, were followed on a monthly basis until death or until study cessation. Life-extending measures (e.g., intubation, feeding tubes) were recorded (as potential surrogate outcomes for death). Autopsies were coordinated by the UCSF Memory & Aging Center. Most brains were examined at UCSF and less frequently by the National Prion Disease Pathology Surveillance Center (NPDPS; Cleveland, OH). The NPDPS was provided brain samples from all autopsies and performed prion typing.

Outcome measures. The primary outcome measure was survival time from randomization to month 2, when the randomized controlled portion of the trial ended. We also conducted secondary survival analyses of survival after the month-2 time point, including the nonrandomized portion of the study. For subjects who were still alive at last follow-up (month 12), date of last contact was used for survival analysis. Life-extending measures, such as feeding tubes and intubation, were recorded for all subjects as possible confounds in the survival analysis. Other secondary measures included scores on functional tests and rating scales (modified Barthel Index, Rankin, CDR, Mini-Mental State Examination [MMSE], and NPI), a quantifiable neurologic examination, neurocognitive testing (see e-Methods for tests), EEG, CSF "biomarkers," and brain MRI.

Statistical analysis. Sample size. We intended to randomize 60 serial subjects with sCJD over 3 years (see e-Results for sample size calculation). Based on survival analysis from compassionate-use quinacrine (supplemental data), we estimated that 30 subjects with sCJD per group would yield an 80% power (α 0.05 level) to detect a doubling of mean survival (0.9 months) from randomization in the quinacrine group compared with the placebo group. Because preliminary data suggested that the modified Barthel score predicted survival independent of treatment, we stratified the randomization by block design based on this score.

Baseline demographic variables, various functional tests and rating scales (MMSE, CDR–Sum of Boxes [CDR–SB], modified Barthel Index, Rankin, and NPI), and neuropsychological testing were compared between treatment groups using independent sample *t* tests for continuous variables and Fisher exact test for noncontinuous variables (tables 1 and 2).

Primary outcome analyses of the randomized portion of the trial. Survival during the first 2 months between treatment groups was analyzed using a log-rank test and associated Cox proportional hazards model, following the intention-to-treat principle. We planned an interim analysis of the survival data halfway through the study using the method of O'Brien and Fleming¹⁴ and an overall error rate of 0.05. These primary statistical analyses were performed using Stata.¹⁵

Secondary analysis of survival. Because subjects returning to UCSF for their month-2 visit were able to choose whether or not to start open-label quinacrine, this eliminated true randomization from this point. We continued accumulating survival data. Survival from randomization to death or end of study was analyzed using a Cox proportional hazards model with a time-dependent treatment group variable.

Secondary outcome analysis. Among the subjects who survived to month 2, we compared changes in the values of the MMSE, CDR–SB, modified Barthel Index, Rankin Scale, and neuropsychological test scores between the baseline and follow-

Table 1 Baseline characteristics by treatment group

Study demographics	Placebo (n = 28)	Quinacrine (n = 23)	p Value ^a
Age at randomization, y, mean ± SD (range)	64.4 ± 10.9 (38-82)	60.5 ± 8.0 (40-75)	0.26
Sex, % female	32	48	0.39
Codon 129 polymorphism, n	27 ^b	23	0.31
MM, %	52	30	
VV, %	11	22	
MV, %	37	48	

Abbreviations: MM = methionine-methionine; MV = methionine-valine; VV = valine-valine.

^aTwo-sample t tests used for age; Fisher exact test used for sex and codon 129.

^bOne subject did not have genetic testing and refused autopsy. For detailed subtyping, see table e-5.

up visits using parametric analysis of covariance for continuous variables and Quade nonparametric analysis of covariance for ordinal variables, adjusting for baseline performance as a covariate, and using PASW 17.0 for Windows (SPSS Inc., Chicago, IL) (table 2).

RESULTS The study enrolled the first subject in April 2005 and stopped enrollment in January 2009. Subjects were formally followed through the study protocol through May 1, 2009 (6 surviving), although data on subject survival were collected through October 15, 2010. In total, 425 patients were referred to the study (figure 1, CONSORT study flow^{16,17}; table e-3).

Subjects: Enrollment, demographics, and baseline characteristics. Sixty-nine subjects consented for the study. Subjects came from across the United States, as well as Canada, with a plurality from California (figure e-1). Eighteen enrolled subjects were considered screen failures and not randomized (see figure 1, table e-4). Fifty-four subjects were randomized to start study drug, but because *PRNP* analysis later identified 3 subjects who carry PrP gene mutations, only 51 subjects with sCJD were included in the survival analysis: 28 in the placebo arm and 23 in the quinacrine arm. No significant differences were found between treatment groups in baseline characteristics, including codon 129 polymorphism, except that the Rankin Scale scores were worse in the quinacrine-treated group (tables 2 and e-5). The 2 groups did not differ significantly on any of the baseline cognitive measures (table 2). Nevertheless, because fewer subjects in the quinacrine treatment group were able to tolerate the full battery of neuropsychological tests at baseline and scored an average of 4 MMSE points lower than the placebo group, a baseline difference in cognitive functioning between the groups cannot be ruled out (see supplemental information).

Primary outcome measure. Per protocol, a midterm survival and adverse event analysis was conducted and no significant survival difference was found. The DSMB recommended study continuation (see e-Results).

Primary analyses. Thirteen of 23 quinacrine subjects (57%) and 19 of 28 placebo subjects (68%) survived to month 2. Figure 2A presents Kaplan-Meier survival curves for both groups for the 2-month randomized, controlled portion of the trial. There was no significant difference in survival between the groups (log-rank statistic, $p = 0.43$; Cox proportional relative hazard = 1.43, quinacrine compared with placebo, 95% confidence interval [CI] = 0.58, 3.53). The hazard ratio itself suggests a survival benefit of placebo over quinacrine, but does not achieve statistical significance; additionally, the wide CI includes values of the hazard ratio less than 1, indicating a survival benefit for quinacrine over placebo as well.

Secondary survival analysis (after month 2). Twenty-six of the 32 surviving subjects (81%; 16/19 in the placebo group and 10/13 in the quinacrine group) returned to UCSF for their month-2 visits (table 3). The entire eligible quinacrine group and all but 2 (14/16) of the eligible placebo group opted to start open-label quinacrine. Because the study was no longer randomized after month 2, we assessed survival differences using time-dependent treatment choices, and censored the 3 subjects who chose life-extending measures. The survival times of subjects who chose quinacrine did not differ significantly from those who did not (Cox proportional hazards model with time-dependent treatment: relative hazard = 0.86; 95% CI = 0.44, 1.70; $p = 0.67$). Adjustment for baseline modified Barthel Index, MMSE or CDR scores, as well as sex, changed the treatment relative hazard only minimally, whereas adjustment for baseline Rankin Scale score reduced the relative hazard to 0.70 (95% CI = 0.36, 1.36). Thus, some of the uncorrected relative hazard for quinacrine was due to the baseline differences between the 2 groups; these results, however, do not indicate statistically significant increased survival for subjects who chose quinacrine compared with those who did not at month 2. To give an impression of the survival experience of the subjects, we divided subjects into 4 groups based on their treatment assignment before and after month 2 and plotted their Kaplan-Meier survival curves (figure 2B).

Table 2 Cognitive and functional scores at baseline in the full cohort and change after 2 months among survivors

Test	Baseline					Change from mo 0 to mo 2 among survivors ^a				
	Placebo		Quinacrine		Cohen d; p value ^b	Placebo		Quinacrine		Adjusted difference; p value ^c
	n = 28	Mean ± SD (range)	n = 23	Mean ± SD (range)		n = 19	Mean ± SD (range)	n = 13	Mean ± SD (range)	
MMSE (0-30) ^d	28	14.1 ± 9.3 (0-29)	23	10.0 ± 10.2 (0-29)	0.42; 0.14	15	-6.9 ± 5.9 (-18 to 4)	9	-3.9 ± 4.9 (-10 to 1)	1.5; 0.54
Barthel Index	28	65.0 ± 29.2 (10-100)	23	60.2 ± 29.8 (5-100)	0.16; 0.59	19	-23.2 ± 35.1 (-85 to 70)	11	-13.2 (-65 to 5)	7.9; 0.36
CDR-SB ^e	28	9.3 ± 4.8 (1-18)	23	12.0 ± 4.5 (4-17)	0.58; 0.06	19	3.2 ± 2.4 (-1 to 8)	12	0.3 ± 0.8 (-1 to 2)	2.8; 0.01 ^f
Rankin Scale ^e	28	3.0 ± 1.0 (1-5)	23	3.6 ± 0.8 (2-5)	0.66; 0.03 ^f	19	0.8 ± 0.7 (0-2)	12	0.3 ± 0.8 (-1 to 2)	0.5; 0.03 ^f
ADAS-Cog (0-70) ^e	19	30.8 ± 13.7 (3-56)	9	29.8 ± 16.7 (5-52)	0.07; 0.87	9	13.0 ± 7.9 (0-23)	4	12.6 ± 17.6 (-2 to 37)	-0.7; 0.92
Phonemic Fluency ^g	22	3.5 ± 4.8 (0-14)	15	3.4 ± 4.2 (0-12)	0.02; 0.95	9	-2.4 ± 3.8 (-8 to 1)	5	-2.2 ± 2.3 (-5 to 0)	0.4; 0.71
Animal Fluency ^g	22	4.7 ± 5.1 (0-20)	15	4.3 ± 4.7 (0-15)	0.08; 0.80	9	-3.2 ± 3.5 (-9 to 2)	5	-2.2 ± 6.6 (-9 to 5)	0.8; 0.70
Digit Span Forward	22	4.4 ± 1.8 (0-8)	14	4.4 ± 1.6 (0-6)	0.00; 0.97	9	-0.2 ± 0.7 (-1 to 1)	5	0.4 ± 1.1 (-1 to 2)	-0.6; 0.22
Digit Span Backward	22	2.2 ± 1.6 (0-5)	14	2.0 ± 1.4 (0-4)	0.13; 0.73	9	-0.7 ± 1.3 (-3 to 1)	5	-0.8 ± 1.9 (-4 to 1)	0.3; 0.72
Symbol Digit Modalities	18	10.3 ± 13.7 (0-46)	9	6.6 ± 7.9 (0-20)	0.33; 0.45	8	-3.6 ± 8.6 (-20 to 8)	3	-4.3 ± 5.1 (-10 to 0)	1.5; 0.80

Abbreviations: ADAS-cog = Alzheimer's Disease Assessment Scale-Cognitive Subscale; CDR-SB = Clinical Dementia Rating-Sum of Boxes; MMSE = Mini-Mental State Examination.

^a Only comparing scores among subjects still alive and able to tolerate cognitive testing at month 2. All measures performed at the University of California, San Francisco visit except if subjects were not able to return for month-2 visit, in which case, Barthel Index, CDR, and Rankin Scale were performed via telephone. For one surviving subject in the quinacrine arm who did not make the month-2 visit, we were unable to obtain remote month-2 follow-up information because they were lost to follow-up at that time. For the second surviving subject, the Barthel Index was inadvertently not performed at month-2 visit. Two subjects, one in each arm, returning to the month-2 visit, did not cooperate fully with the MMSE, which was therefore not scored and not included.

^b The p values were derived from independent sample t tests for continuous variables and Fisher exact test for noncontinuous (ordinal) variables, such as the modified Barthel Index, CDR-SB, and the Rankin Scale score.

^c The difference between change scores, adjusted for month-0 performance. Positive adjusted differences indicate greater adjusted change (worsening) in the placebo group; negative differences indicate greater adjusted change (worsening) in the quinacrine group. The p values were derived from analysis of covariance for continuous variables and from Quade rank analysis of covariance for the Barthel Index, CDR-SB, and Rankin Scale. Greater worsening of CDR-SB and Rankin Scale scores was seen in the placebo group compared with the quinacrine group after the adjustment for baseline scores. No other adjusted change scores were significant.

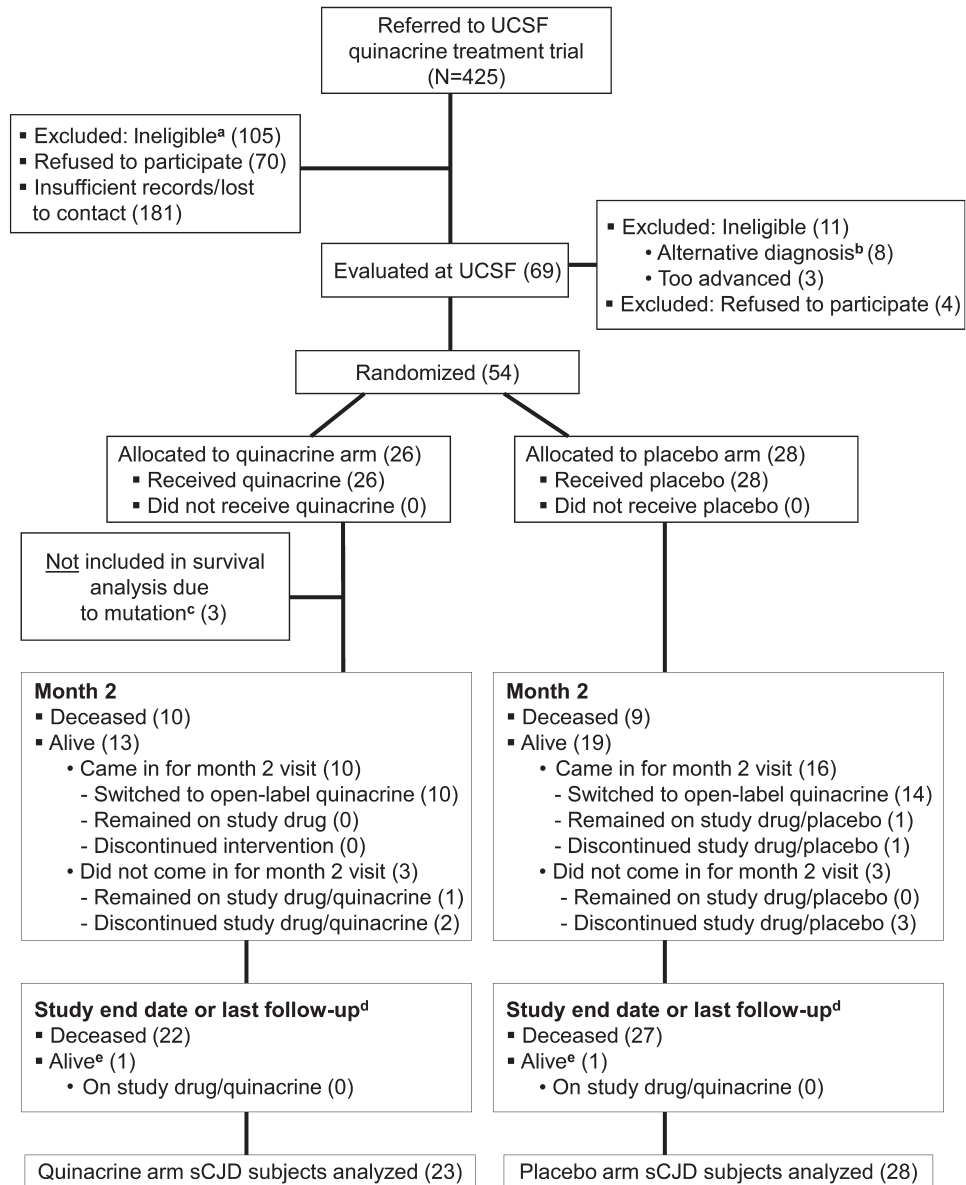
^d One subject in the placebo group was administered only 25 items on the MMSE because of visual impairment, and this subject's score was scaled based on percentage correct.

^e For these scales, a higher value and/or a positive change is worse.

^f A significant difference was found for the Rankin Scale score only, which was worse in the quinacrine group, although the CDR trended toward being worse as well.

^g Number of D words or animals generated in 1 minute.

Figure 1 Quinacrine CJD treatment trial flowchart



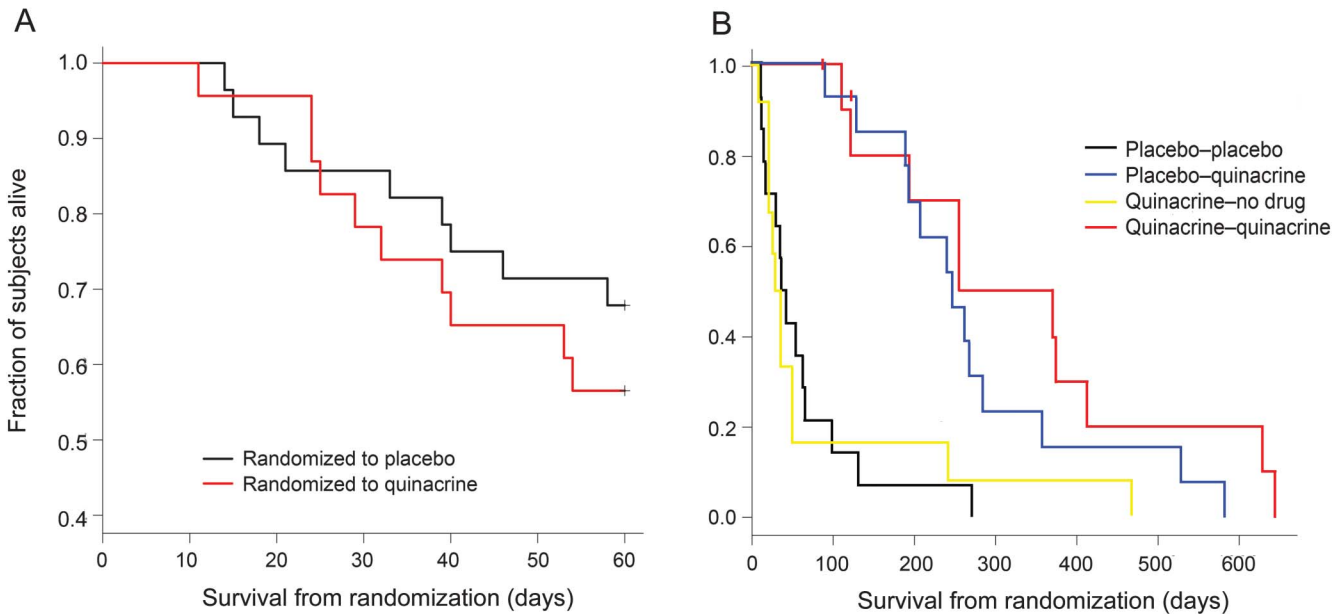
^a Ineligible includes referred subjects who did not meet inclusion criteria (e.g., had an alternative diagnosis, were too advanced to participate [could not follow simple commands and swallow], did not live in the United States or Canada, had no caregiver, or did not fulfill other inclusion criteria). Many potential or probable sCJD referrals did not want to participate in research, did not respond to follow-up, died before evaluation, were unable to travel, or did not wish to prolong life. ^b Includes one subject who was given a clinical diagnosis of possible Sprue and did not wish to have a brain biopsy to confirm CJD. The subject was therefore not randomized. Autopsy later revealed a diagnosis of sCJD. ^c Three subjects, who were originally randomized to the quinacrine arm, were clinically diagnosed with probable sCJD, but genetic results revealed one fCJD (D178N) case, one case with 9-OPRI mutation, and one fCJD (V180I) case. ^d Although formal study follow-up was discontinued on May 1, 2009, some families remained in contact with the research team after that date. These numbers reflect the number of subjects that were still alive at last contact as of October 15, 2010. ^e Two subjects, one in each arm, were still alive as of the last follow-up, but were both receiving life-extending measures. CJD = Creutzfeldt-Jakob disease; fCJD = familial CJD; 9-OPRI = 9 octapeptide repeat insertion; sCJD = sporadic CJD; UCSF = University of California, San Francisco.

Secondary outcome measures analysis. In surviving patients at month 2, controlling for baseline performance, the quinacrine-treated group showed less decline than the placebo group on the CDR-SB and the modified Rankin Scale, but not the Barthel Index. For subjects able to undergo neurocognitive testing at month 2, controlling for baseline performance,

there were no significant differences between groups in the change in scores between month 0 and month 2 on any of the cognitive tests (table 2; all *p* values >0.05).

Adverse events. We examined AEs and SAEs in 2 timeframes: 1) through month 2, placebo arm vs quinacrine

Figure 2 Kaplan-Meier survival analysis from baseline to month 2 and to death



(A) Kaplan-Meier survival analysis from month 0 (baseline) to month 2 for 51 randomized subjects with sCJD (placebo, $n = 28$; quinacrine, $n = 23$). These differences were not statistically significant (log-rank statistic, $p = 0.43$; Cox proportional relative hazard = 1.43 quinacrine compared with placebo, 95% confidence interval = 0.58, 3.53). (B) Kaplan-Meier survival analysis from baseline to death or date of life-extending measures (censored) or to date of last contact (censored) for 51 randomized subjects with sCJD. Four groups were based on the treatment arm at randomization and the treatment arm chosen at month 2, to obtain the placebo-placebo group ($n = 5$); the placebo-quinacrine group ($n = 14$); the quinacrine-placebo group ($n = 3$); and the quinacrine-quinacrine group ($n = 10$). Because groups in this figure are not based solely on randomization, but include subject choice at month 2, we did not conduct a formal statistical test of differences in survival. Note that these curves might appear to suggest a greater benefit of quinacrine than the data indicate, as the subjects who went on open-label quinacrine were survivors (and most in good enough condition to return for their month-2 visit) from the placebo and quinacrine groups. sCJD = sporadic Creutzfeldt-Jakob disease.

arm, and 2) after month 2, divided into those occurring within, vs outside of, 30 days of taking quinacrine. The number of AEs and the number of subjects with AEs through month 2 were similar between arms; the types of AEs differed, however. For example, elevated liver function tests were only seen in the quinacrine arm (table e-6). Through month 2, each arm had 3 SAEs, all different between arms (table e-7). Only one SAE, severe gastrointestinal distress, was assessed to be possibly due to quinacrine. Twenty-two percent of quinacrine arm and 18% of placebo arm subjects required dose reduction through month 2. After month 2, there were many more AEs and subjects with AEs within 30 days of taking quinacrine; more than half involved elevated liver function tests (12/27) or gastrointestinal distress (5/27). Of the 6 SAEs after month 2, 5 occurred within 30 days of taking quinacrine, but only one (behavioral change) was determined to be possibly or likely due to quinacrine. Overall, quinacrine was reasonably well tolerated.

DISCUSSION This interventional study provides Class I evidence that oral quinacrine (300 mg per day) over a 2-month period did not prolong survival of subjects with sCJD. Time-dependent survival analysis corroborated findings of the randomized portion

of the trial, showing no difference in survival based on whether subjects were receiving quinacrine or not. Although quinacrine has been shown to eliminate prions *in vitro*, the present findings do not support a favorable survival response in human prion disease, consistent with observational analyses of quinacrine in human prion disease^{18–20} and animal studies.^{21–23}

The failure of quinacrine to extend survival in our study might be attributable to several reasons, including insufficient concentrations in the appropriate cellular compartment, inefficacy *in vivo*, as well as study design and limitations. Whereas our initial findings in cell culture^{3,24} and the long experience with quinacrine as anti-malarial^{7,25,26} made it an exciting candidate for CJD treatment, our findings in humans are consistent with the disappointing results of several early animal studies.^{21,22,27} From our own and other studies,^{24,28–30} we concluded that a conformational change in the RML prion strain allowed it to replicate in the presence of high levels of quinacrine³¹ (see e-Discussion).

Quinacrine and some analogs have been studied by binding to recombinant human PrP (recHuPrP) (90–231) in the presence of SH-SY5Y cells.³² In these studies, the recHuPrP (90–231) was denatured at 53°C for 1 hour and then exposed to quinacrine or an analog. Quinacrine was more effective in rendering recHuPrP

Table 3 Month-2 follow-up, open-label choice, and survival^a

	Assigned treatment arm at randomization	
	Placebo	Quinacrine
No.	28	23
Alive at mo 2, % (n)	68 (19/28)	57 (13/23)
Came to mo-2 visit, % (n)	84 (16/19)	77 (10/13) ^b
Switched to open-label quinacrine at mo 2, % (n) ^c	88 (14/16) ^d	100 (10/10)
Alive at mo 6, % (n)	46 (13/28)	48 (11/23)
Came to mo-6 visit, % (n)	15 (2/13)	18 (2/11)
Survival from randomization, mo ^a		
Mean	5.6	6.6
Median	4.3	3.8
Range	0.5-19.6	0.4-21.6
Survival from first symptom, mo ^a		
Mean	17.4	19.3
Median	17.2	15.5
Range	1.7-42.2	3.3-57.7

^aSurvival based on dates of last contact for 2 subjects as of October 15, 2010 (see figure 1). Three subjects (1 in the placebo arm and 2 in the quinacrine arm) used feeding tubes or ventilators to extend life; for these 3 subjects, initiation date of life-extending measures was used as date of death for survival duration.

^bOf the 3 subjects who did not come back for their month-2 visit, 2 had already discontinued study drug (one because of behavioral issues and the other because of unexplained lung and hepatic lesions; medical workup, including biopsy, did not reveal any cancer or other etiology; subject refused autopsy). The third subject remained on study drug.

^cOnly those who came to month-2 visit were offered open-label quinacrine.

^dOf the 2 subjects who did not switch to open-label quinacrine, one had discontinued study drug before month 2 because of behavioral issues thought by family to be adverse side effects of study drug and the other subject chose to remain on the study drug.

(90–231) susceptible to limited proteinase K digestion than most analogs, but was only marginally effective in protecting SH-SY5Y cells from the toxic effects of recHuPrP (90–231). Interestingly, one quinacrine analog, 6-chloro-2-methoxy-9-[[[(1S,9aR)-(octahydro-2H-quinolizin-1-yl)methyl]amino]acridine (Q3), was quite effective in preventing the toxicity of recHuPrP (90–231).

It is possible that even though adequate total brain quinacrine concentrations were achieved,^{23,33} quinacrine levels in the extracellular compartment, where PrP^{Sc} resides on cell membranes, were too low.²¹ Although the anti-prion mechanism of quinacrine action in ScN2a cells is unknown, some investigators argue that quinacrine works through binding to PrP^C.³⁴ In other studies, we found that quinacrine inhibits PrP^{Sc} in dividing ScN2a cells but not in nondividing cells.²³ Whether or not reductions in PrP^{Sc} levels in nondividing cells will be predictive of efficacy in vivo for putative prion therapeutics remains to be established.

It is notable that the vast majority of neurons in the adult CNS do not divide. Whether drug-resistant

prions are more likely to emerge in nondividing cells is unknown, but conformational transformation in PrP^{Sc} followed by selection in cell culture is now well documented.^{31,35} Curiously, 2 subjects, both in the quinacrine arm, were clearly thought to have improved by their caregivers and study staff during the first 2 months of the study; both subjects also had slight improvement on scales and cognitive testing (see supplementary material). Because these and other subjects eventually declined after month 2, these improvements might have been due to the psychoactive side effects of quinacrine^{5,6,36} or due to a temporary reduction in prion load, as has been shown in mouse prion models treated with quinacrine. It appears that quinacrine, both in vitro and in vivo, might reduce PrP^{Sc} initially, but continuous treatment results in strain selection of PrP^{Sc} that is resistant to the effects of quinacrine.²³

Although quinacrine did not prolong survival in this study, the quinacrine group showed less decline in 2 functional outcomes during the initial 2-month randomized phase of the study. The clinical significance of this is unclear as there were no differences in decline on a third functional scale or on any cognitive measures. Although we believe that prolonged survival is probably the most important first outcome for treating prion disease, preservation of or improvement in cognition or function might be viable targets in future CJD treatment trials. In fact, the flupirtine treatment trial in sCJD used cognition as the primary outcome.²

There were several limitations to this study. First, the study sample size was small although we enrolled a large number of subjects (n = 69) for such a rare disease. The final sample size of 51 subjects led to wide variability in estimates of the survival difference. Second, the study design, allowing subjects who came back to UCSF for their month-2 visits to switch to open-label quinacrine, restricted the true randomization period to the first 2 months. There also were significant limitations to the matching of groups after the month-2 time point. Although we adjusted for the fact that some subjects switched treatment arms at month 2 by using a time-dependent survival analysis, these data are influenced by many confounding factors. For example, only subjects who returned for their month-2 visit could elect to switch to open-label quinacrine. This group consisted of subjects who were able to travel, whereas most subjects who did not return probably were more impaired. Third, the treatment arms were not as matched as we anticipated; the quinacrine arm had significantly lower Rankin Scale scores. This difference was subsequently discovered to be due to a procedural error (see supplemental data for details). We do not believe that this significantly affected the study conclusions.

This represents the first report of a Class I treatment study of survival in sCJD. Although the outcome was negative, this study has shown that appropriate randomized controlled trials can be performed in rare, rapidly progressive, uniformly fatal neurodegenerative diseases. Methodologies are now in place for future trials. As with MRC PRION1,¹⁸ which was an observational trial of quinacrine in prion disease, we now have data quantifying the course of prion disease (manuscript in preparation), which will be essential for future prion trials.

As shown by baseline characteristics, our patients had significant cognitive and functional impairment at randomization. Earlier diagnosis of prion disease is probably necessary for potential treatments to have benefit and thus should be a goal of prion research along with finding new treatments. Given the rarity of prion disease, multinational trials, possibly with other study designs such as delayed start, should be considered in the future for faster enrollment and data collection.

AUTHOR CONTRIBUTIONS

M.D. Geschwind: study concept and design, acquisition of data, analysis and interpretation, critical drafting and revision, study supervision. A.L. Kuo: acquisition of data, analysis and interpretation, critical drafting and revision, study supervision. K.S. Wong: acquisition of data, analysis. A. Haman: acquisition of data and analysis and interpretation, critical drafting and revision, study supervision. G. Devereux: acquisition of data, critical drafting and revision, study supervision. B.J. Raudabaugh, D.Y. Johnson, and C.C. Torres-Chae: acquisition of data, analysis. R. Finley: study concept and design, acquisition of data. P. Garcia: study concept and design, acquisition of data, analysis. J.N. Thai: acquisition of data, analysis. H.Q. Cheng: study concept and design, acquisition of data, critical drafting and revision. J.M. Neuhaus: study concept and design, analysis and interpretation, critical drafting and revision. S.A. Forner: acquisition of data, analysis and interpretation. J. Duncan: study concept and design, acquisition of data. K.L. Possin: analysis and interpretation, critical drafting and revision. S.J. DeArmond: study concept and design, acquisition of data. S.B. Prusiner: study concept and design, analysis and interpretation, critical drafting and revision. B.L. Miller: study concept and design, acquisition of data, analysis and interpretation, critical drafting and revision, study supervision.

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Quinacrine treatment trial for sporadic Creutzfeldt-Jakob disease

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