Six-Month Randomized, Placebo-Controlled, Double-Blind, Pilot Clinical Trial of Curcumin in Patients With Alzheimer Disease

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Patients were eligible for this double-blind, placebo-controlled, randomized, 6-month trial if they were 50 years old or older, ethnic Chinese in Hong Kong, had progressive decline in memory and cognitive function for 6 months, had National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer Disease and Related Disorders Association diagnosis of probable or possible AD,[13] and gave written informed consent. For subjects unable to understand the study and their role in it, consent was obtained from the caregivers. Exclusion criteria were anticoagulant or antiplatelet treatment or bleeding risk factors, current smoking, or severe illness making study completion unlikely. The study was

approved by the Hong Kong Clinical Research Ethics Committees for New Territories East and Kowloon West and followed the Helsinki Declaration. Thirty-four patients were recruited: 9 from old age homes and 24 from dementia clinics. When the trial period was nearing conclusion, 2 additional patients were recruited but could only be treated and monitored for 1 month. Patients were randomized to 4, 1 (plus 3 g color-matched placebo powder), or 0 g of curcumin (plus 4 g of placebo) once daily, with stratification by their prestudy Cantonese MMSE[14] score range (<14, 14–17, or >17) to improve matching of baseline scores among dose groups. Of 22 patients randomized to 4 or 1 g, 10 patients chose to take curcumin/placebo as 10 capsules to swallow after a meal; and 12 patients, as a packet of powder to mix with food. Patients were permitted to continue (or to change at any time) any treatment deemed appropriate by their physicians and were also given as a standard treatment, which showed moderate benefit in previous studies, 1 capsule/d 120 mg standardized ginkgo leaf extract (Shanghai Charoma, Shanghai, China).[15] Curcumin was given by Kancor Flavours, Kerala, India, for packets, or bought from Arjuna Natural Extracts, Kerala, India, for capsules.

At 0, 1, and 6 months, plasma was taken to measure isoprostanes $iPF_{2\alpha}$-III and antioxidants, and so was serum to monitor Aβ and liver and kidney function. At 1 month, plasma was taken to assay curcumin and metabolites. Mini-Mental State Examination was administered at baseline and 6 months. Amyloid β_{40} was measured by enzyme-linked immunosorbent assay (Covance, Dedham, Mass). Curcumin is a mixture of 3 similar molecules—curcumin, demethoxycurcumin, and bisdemethoxycurcumin (CDB), the former being most abundant. Curcumin, demethoxycurcumin, bisdemethoxycurcumin, tetrahydrocurcumin, ferulic acid, vanillic acid, and vanillin were measured in plasma by liquid chromatography–mass spectrometry-mass spectrometry[12] after β-glucuronidase treatment (Sigma, St Louis, Mo). To measure isoprostanes, blood was collected in lithium-heparin tubes with 15 μM of indomethacin. Butylated hydroxytoluene was added to plasma to 20 μM. Isoprostanes were enriched by an affinity column and measured by gas chromatography–mass spectrometry. High-performance liquid chromatography assays measured antioxidants: plasma glutathione peroxidase and superoxide dismutase activity, ascorbic acid, uric acid, and vitamins A and E.[16,17] Statistics were calculated using SPSS 11.5 (SPSS Inc, Chicago, Ill). Continuous variables were compared by testing for normality (Kolmogorov-Smirnov test) and then analysis of variance or *t* test for normal distributions and Wilcoxon or Mann-Whitney *U* test otherwise. Discrete variables were compared using χ^2 test.

Thirty-four subjects began the 6-month trial. Of 27 finishing it with less than 30 cumulative days off the study drug (8 subjects on 0 g, 8 on 1 g, and 11 on 4 g), baseline clinical measures were matched across dose groups: ages (mean ± SD) were 77.8 ± 7.7 years on 0 g, 69.0 ± 10.9 on 1 g, and 73.4 ± 6.6 on 4 g ($P = 0.14$); male subjects were 3 of 8 on 0 g, 1 of 8 on 1 g, and 3 of 11 on 4 g ($P = 0.52$); and MMSE scores (mean ± SD) were 15.4 ± 5.8 on 0 g, 15.4 ± 5.0 on 1 g, and 15.6 ± 7.9 on 4 g ($P = 1.0$). Of the other 7 subjects, 0 were on 4 g/d curcumin, 3 on 1 g, and 4 on 0 g ($P = 0.11$); 3 withdrew for gastrointestinal complaints, 3 for falls or dizziness, and 1 for respiratory tract infection. To monitor safety, sodium, potassium, urea, creatinine, protein, albumin, bilirubin, alkaline phosphatase, and alanine aminotransferase/glutamic-pyruvic transaminase were measured, but any toxicity not affecting these values might have been missed. Changes in none of the values between baseline and 6 months differed significantly among dose groups. Adverse events totaled 7 on 0 g, 6 on 1 g, and 2 on 4 g: 4 gastrointestinal (2 on 0 g, 2 on 1 g, and 1 on 4 g), 3 respiratory tract infections (2 on 0 g and 1 on 1 g), 3 falls or dizziness (1 on 0 g, 1 on 1 g, and 1 on 4 g), 2 delusional (1 on 1 g and 1 on 4 g), 2 edema (1 on 0 g and 1 on 1 g), and 1 hearing impairment (on 0 g). Power was 14% to detect an α of 0.05 difference between curcumin and 0 g in MMSE changes of the same effect size as a 24-week donepezil study.[18]

Changes in MMSE scores between 0 and 6 months were compared among dose groups, either including (mean ± SE, 1.3 ± 0.6 on 0 g; −0.6 ± 1.0 on 1 g; and 0.7 ± 1.1 on 4 g; $P = 0.43$) or excluding ($P = 0.37$) patients on vitamin E or standard AD drugs, and between 0 g and curcumin (mean ± SE, 1.3 ± 0.6 on 0 g; 0.2 ± 0.7 on curcumin; $P = 0.39$) for patients using capsules (mean ± SE, 1.5 ± 0.7 on 0 g, −0.2 ± 1.3 on curcumin; $P = 0.34$) or packets (mean ± SE, 0.0 ± undefined on 0 g; 0.5 ± 0.8 on curcumin; $P = 0.86$). Serum $A\beta_{40}$ levels (Fig. 1) did not differ among doses at 0 ($P = 0.63$), 1 ($P = 0.78$), or 6 months ($P = 0.36$). Between baseline and 6 months, serum $A\beta_{40}$ (mean ± SE) changed from 30 ± 6 ng/L to 26 ± 3 on 0 g and from 28 ± 6 to 35 ± 7 on 4 g ($P = 0.15$). The change in serum $A\beta_{40}$ between baseline and 1 month did not differ between patients taking curcumin as capsules (mean ± SE, 26 ± 18%) or powder (mean ± SE, 27 ± 22%; $P = 0.66$). The change in plasma isoprostanes (mean ± SE) between baseline and 6 months did not differ among doses ($P = 0.23$): −11 ± 10% for 0 g, 12 ± 10% for 1 g, and 6 ± 8% for 4 g. The change in isoprostanes between baseline and 6 months did not differ between patients taking curcumin as capsules (mean ± SE, 15 ± 7%) or powder (mean ± SE, 4 ± 9%; $P = 0.43$). Over 1 month, vitamin E levels changed, 1 ± 3% with curcumin (8 ± 2% for capsules vs −4 ± 5% for powder; $P = 0.05$) versus −21 ± 5% with 0 g ($P = 0.001$), and the percent change of vitamin E levels correlated positively with the total curcuminoid level ($P = 0.01$; Pearson correlation); patients taking vitamin E supplements were excluded.

In a preliminary experiment, curcumin was measured in plasma from 1 nondemented control subject at various times after 4 g of curcumin either with or without food. No signal was detected unless the plasma was first treated with glucuronidase, demonstrating that nearly all the curcumin was glucuronidated. The level of curcumin (CDB) peaked at 250 nM at 1.5 hours with food and at 270 nM at 4 hours with only water. At 24 hours, the level fell to 60 nM. Based on these findings, we decided to measure curcumin 2 to 2.5 hours after ingestion. There were no significant differences in levels of any curcuminoids or of total curcuminoids between 1- and 4-g groups; thus, both groups

were pooled for calculating mean ± SE (in nanomolar) levels: 250 ± 80 curcumin, 150 ± 50 demethoxycurcumin, 90 ± 30 bisdemethoxycurcumin, 440 ± 100 tetrahydrocurcumin, 110 ± 20 ferulic acid, 50 ± 20 vanillic acid, 490 ± 160 CDB, and 1100 ± 260 total curcuminoids. No vanillin was detected in any samples. One patient receiving 1 g/d had total curcuminoid levels 2.8 times as high as any other patient, and when this patient was excluded, total curcuminoid levels tended to be greater with 4 g than with 1 g ($P = 0.15$): 1040 ± 150 versus 650 ± 210. Patients taking capsules (taken fasting with water; 10 patients) had greater levels of CDB than did patients taking powder (with a little food; 12 patients): 940 ± 290 versus 120 ± 40; $P = 0.02$. However, levels of tetrahydrocurcumin, ferulic acid, or vanillic acid did not differ between patients on capsules or powder.

DISCUSSION

As the first study published on curcumin treatment of AD patients, this trial provided data on side effects, drug absorption, and biological effects. Curcumin may act in AD by several possible mechanisms, including Aβ disaggregation, anti-inflammation, and antioxidation.[2,3,7,8,19] The lack of cognitive decline on placebo in this 6-month trial may have precluded any ability to detect a relative protective effect of curcumin, which presumably would have appeared as a slower decline rather than an improvement in cognition. A study of longer duration, with a more sensitive test such as the Alzheimer Disease Assessment Scale–cognitive subscale and perhaps less treatment by other AD drugs, may show greater deterioration on placebo.

The greater level of curcumin but not tetrahydrocurcumin, ferulic acid, or vanillic acid after capsules than powder may be due to more absorption and less metabolism of curcumin from capsules, suggesting that capsules be used in future trials. The lack of difference in curcumin or metabolite levels between 1- and 4-g groups suggests that there may be no need to exceed 1 g in future trials. Curcumin prevents or reverses half of the aggregation (IC_{50}) of Aβ at 0.2 to 1 μM CDB.[7,8] In this study, mean plasma CDB was 490 nM (940 nM for capsules). A study in mice found that curcumin reached similar concentrations in the brain as in plasma: 0.41 μg/g in brain and 0.60 μg/g in plasma.[12] Thus, curcumin may reach brain concentrations sufficient to decrease Aβ aggregation. Metabolites of curcumin might contribute further; the IC_{50} of ferulic acid is 2 to 10 μM, and tetrahydrocurcumin has not yet been tested.[20]

Plasma antioxidants, including glutathione peroxidase and superoxide dismutase activity; uric acid; and vitamins A, C, and E, were reportedly decreased in AD.[11] We found that curcumin raised vitamin E. One interpretation is that the antioxidant activity of curcuminoids might decrease need for and depletion of the antioxidant vitamin E. Another possibility is that curcumin slows AD progression, reducing oxidation because of processes within the AD brain.

Although serum $Aβ_{40}$ levels did not differ significantly among doses, serum $Aβ_{40}$ tended to rise on curcumin, possibly reflecting an ability of curcumin to disaggregate Aβ deposits in the brain, releasing the Aβ for circulation and disposal.[7,8]

Curcumin did not seem to cause side effects in AD patients (rather, there was a tendency toward fewer adverse events on 4 g). Thus, longer and larger trials to test the efficacy of curcumin for treating AD may be safely commenced.

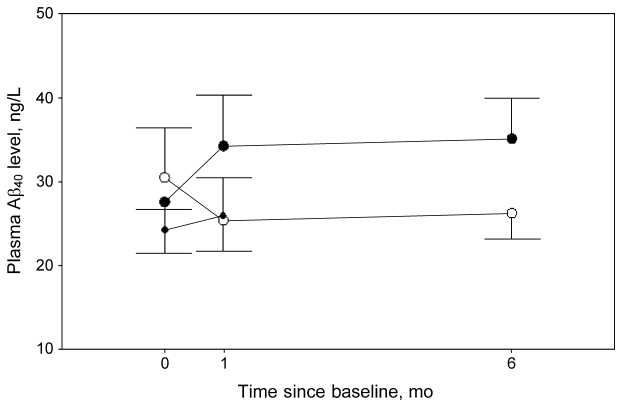

FIGURE 1. Mean ± SE plasma $Aβ_{40}$ levels in dose groups among subjects completing the 6-month study: placebo (open circles), 1 g/d curcumin (small closed circles), and 4 g/d curcumin (large closed circles).

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REFERENCES

1. Araujo CC, Leon LL. Biological activities of Curcuma longa L. *Mem Inst Oswaldo Cruz*. 2001;96:723–728.
2. Frautschy SA, Hu W, Kim P, et al. Phenolic anti-inflammatory antioxidant reversal of Abeta-induced cognitive deficits and neuropathology. *Neurobiol Aging*. 2001;22:993–1005.
3. Lim GP, Chu T, Yang F, et al. The curry spice curcumin reduces oxidative damage and amyloid pathology in an Alzheimer transgenic mouse. *J Neurosci*. 2001;21:8370–8377.
4. Ng TP, Chiam PC, Lee T, et al. Curry consumption and cognitive function in the elderly. *Am J Epidemiol*. 2006;164:898–906.
5. Solfrizzi V, D'Introno A, Colacicco AM, et al. Circulating biomarkers of cognitive decline and dementia. *Clin Chim Acta*. 2006;364:91–112.
6. Buxbaum JD, Cullen EI, Friedhoff LT. Pharmacological concentrations of the HMG-CoA reductase inhibitor lovastatin decrease the formation of the Alzheimer beta-amyloid peptide in vitro and in patients. *Front Biosci*. 2002;7:A50–A59.
7. Ono K, Hasegawa K, Naiki H, et al. Curcumin has potent anti-amyloidogenic effects for Alzheimer's beta-amyloid fibrils in vitro. *J Neurosci Res*. 2004;75:742–750.
8. Yang F, Lim GP, Begum AN, et al. Curcumin inhibits formation of amyloid beta oligomers and fibrils, binds plaques, and reduces amyloid in vivo. *J Biol Chem*. 2005;280:5892–5901.
9. Montine TJ, Quinn JF, Montine KS, et al. Quantitative in vivo biomarkers of oxidative damage and their application to the diagnosis and management of Alzheimer's disease. *J Alzheimers Dis*. 2005;8:359–367.
10. Pratico D, Clark CM, Liun F, et al. Increase of brain oxidative stress in mild cognitive impairment: a possible predictor of Alzheimer disease. *Arch Neurol*. 2002;59:972–976.
11. Rinaldi P, Polidori MC, Metastasio A, et al. Plasma antioxidants are similarly depleted in mild cognitive impairment and in Alzheimer's disease. *Neurobiol Aging*. 2003;24:915–919.
12. Pan MH, Huang TM, Lin JK. Biotransformation of curcumin through reduction and glucuronidation in mice. *Drug Metab Dispos*. 1999;27:486–494.
13. McKhann G, Drachman D, Folstein M, et al. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology*. 1984;34:939–944.
14. Chiu HFK, Lee HC, Chung WS, et al. Reliability and validity of the Cantonese version of the Mini-Mental State Examination—a preliminary study. *J Hong Kong Coll Psychiatrists*. 1994;4(suppl 2):25–28.
15. Mazza M, Capuano A, Bria P, et al. Ginkgo biloba and donepezil: a comparison in the treatment of Alzheimer's dementia in a randomized placebo-controlled double-blind study. *Eur J Neurol*. 2006;13:981–985.
16. Ip SP, Ko KM. The crucial antioxidant action of schisandrin B in protecting against carbon tetrachloride hepatotoxicity in mice: a comparative study with butylated hydroxytoluene. *Biochem Pharmacol*. 1996;52:1687–1693.
17. Ross MA. Determination of ascorbic acid and uric acid in plasma by high-performance liquid chromatography. *J Chromatogr B Biomed Appl*. 1994;657:197–200.
18. Feldman H, Gauthier S, Hecker J, et al. A 24-week, randomized, double-blind study of donepezil in moderate to severe Alzheimer's disease. *Neurology*. 2001;57:613–620.
19. Baum L, Ng A. Curcumin interaction with copper and iron suggests one possible mechanism of action in Alzheimer's disease animal models. *J Alzheimers Dis*. 2004;6:367–377.
20. Ono K, Hirohata M, Yamada M. Ferulic acid destabilizes preformed beta-amyloid fibrils in vitro. *Biochem Biophys Res Commun*. 2005; 336:444–449.