Effects of a Behavioral Intervention, Tai Chi Chih, on Varicella-Zoster Virus Specific Immunity and Health Functioning in Older Adults

MICHAEL R. IRWIN, MD, JENNIFER L. PIKE, PHD, JASON C. COLE, PHD, AND MICHAEL N. OXMAN, MD

Objective: Both the incidence and severity of herpes zoster (shingles) increase markedly with increasing age in association with a decline in varicella-zoster virus (VZV) specific cell-mediated immunity (CMI). This study examined whether a behavioral intervention, Tai Chi Chih (TCC), affects VZV specific immunity and health functioning in older adults who, on average, show impairments of health status and are at risk for shingles. **Methods:** Thirty-six men and women (age ≥60 years) were assigned randomly to a 15-week program of TCC instruction (three 45 minute classes per week; $N = 18$) or a wait list control condition ($N = 18$). VZV-specific CMI was measured at baseline and at 1-week postintervention. Health functioning (Medical Outcome scale: SF-36) was assessed at baseline, and at 5, 10, and 15 weeks during the intervention, and at 1-week postintervention. **Results:** In the intent-to-treat sample, VZV-specific CMI increased 50% from baseline to 1-week postintervention in the TCC group ($p < 0.05$) but was unchanged in the wait list control group. In those who completed the study, 1-week postintervention SF-36 scale scores for role-physical ($p < 0.05$) and physical functioning ($p < 0.05$) were higher in the TCC group ($N = 14$) as compared with controls ($N = 17$). Older adults who had impairments of physical status at baseline showed the greatest increases of SF-36 role-physical ($p < 0.01$) and physical functioning ($p < 0.001$) during the TCC intervention. **Conclusions:** Administration of TCC for 15 weeks led to an increase in VZV-specific CMI. Gains in health functioning were found in participants who received TCC and were most marked in those older adults who had the greatest impairments of health status. **Key words:** psychoneuroimmunology, alternative medicine, immunity, aging, shingles, health functioning.

ANOVA = analysis of variance; **CMI** = cell-mediated immunity; **HBSS** = Hanks Balanced Saline Solution; **HZ** = herpes zoster; **PBMC** = peripheral blood mononuclear cells; **RCF** = responder cell frequency; **SF-36** = Medical Outcomes Study short form; **TCC** = Tai Chi Chih; **VZV** = varicella zoster virus.

INTRODUCTION

Both the incidence and severity of HZ or shingles increase markedly with increasing age (1–3), and this has been attributed to a decline in CMI to VZV (4). VZV-specific CMI, a critical component of memory immunity, is required to protect against symptomatic reinfection after new exposure to the virus and to inhibit reactivation of latent virus (5). In contrast, the presence of anti-VZV antibodies that provide evidence of prior infection and anti-VZV immunity do not have an essential role in the prevention or recovery from infection (6).

Older adults show considerable heterogeneity in their levels of VZV-specific CMI, as well as in other aspects of cellular immunity (7), and the factors that account for this variability and for the increased risk of HZ in older adults are not well understood. Within populations, individual differences in physical or emotional functioning have been implicated. Indeed, Schmader et al. found that psychological stress in the elderly is associated with the occurrence of HZ (8), whereas major depressive disorder is associated with a decline in VZV-specific CMI (9) as measured by VZV-RCF. VZV-RCF reflects the frequency of memory T lymphocytes that respond to VZV antigens in vitro and serves to quantitate VZV specific CMI and, possibly, to define risk for HZ (6).

Behavioral intervention trials provide experimental evidence that behavioral and psychological processes influence the immune system, with potential effects on immune-mediated disease (10). For example, writing about a traumatic event reduces emotional distress and is associated with improvements of overall disease activity in patients with asthma or rheumatoid arthritis (11) and with augmented antibody responses to hepatitis B vaccination in healthy volunteers (12). Similarly, a comprehensive psychoeducational intervention in malignant melanoma patients reduces symptoms of depression and anxiety and is associated with increases in natural immunity and decreased mortality in a 6-year follow-up study (13, 14). While these data have generated considerable interest and have implications for the field of psychoneuroimmunology, a recent meta-analytic review suggests that the findings noted above might not be representative of the literature as a whole (10). Multiple factors may contribute to these inconsistent observations including, as suggested by Miller and Cohen (10), the enrollment of healthy participants rather than persons at risk of immune alterations (eg, aged or chronically stressed) (15); the use of behavioral strategies in which training standardization and implementation (ie, frequency of relaxation practice) were variable, or the use of immune measures that were nonspecific or for which clinically relevant disease endpoints had not been determined (10).

In older adults, HZ can result in considerable disability and declines of both physical and emotional quality of life (1–3). Novel interventions that might boost VZV-specific CMI and also improve multiple aspects of health functioning in this at-risk population are needed. This study hypothesizes that TCC is one such intervention. TCC is a westernized version of Tai Chi Chuan, an exercise form that has existed as a martial art in the Chinese culture for >2000 years and as an exercise for elderly people for >300 years (16). As a standardized series of 20 simple, repetitive, nonstrenuous movements, TCC is designed for use in the elderly and medically compromised

From the Cousins Center for Psychoneuroimmunonology (M.R.I., J.L.P., J.C.C.), UCLA Neuropsychiatric Institute, University of California, Los Angeles; and Department of Medicine (M.N.O.), University of California, San Diego and San Diego Veterans Affairs Healthcare System, San Diego, California.

Address reprint requests to: Michael Irwin, MD, Department of Psychiatry and Biobehavioral Sciences, Cousins Center for Psychoneuroimmunology, University of California, Los Angeles, 300 UCLA Medical Plaza, Suite 3-109, Los Angeles, CA 90095-7057. Email: mirwin1@ucla.edu

Received October 19, 2002; revision received February 19, 2003.
DOI: 10.1097/01.PSY.0000088591.86103.8F

0033-3174/03/6505-0824

populations. Randomized, controlled trials suggest that TCC can improve health functioning, have effects on both physical and emotional health (16), reduce the risk of falls (17, 18), and possibly enhance cardiovascular functioning in older adults (16, 19, 20). The immunologic effects of this "meditation through movement" have not yet been evaluated. In an attempt to assess the effects of TCC on clinically relevant immune function, older adults were randomized to either TCC or a wait list control group and then evaluated to determine whether TCC affected VZV-specific immunity. In addition, in light of prior findings on TCC and health functioning in the elderly (21), we examined the effects of TCC on health status and also explored whether TCC might be most effective in those at-risk older adults who had the greatest health impairments.

METHODS

Subjects

Participants were volunteers recruited from the La Jolla and San Diego communities who responded to advertisements posted in local newspapers and newsletters, seeking older adults to "participate in a study of Tai Chi Chih and immunity." Interested participants were screened by telephone to determine eligibility. Inclusion criteria were as follows: 60 years of age or older at time of entry, geographically accessible, and history of varicella (chickenpox) or long-term (≥30 years) residence in the continental United States. The latter two inclusion criteria are indicative of prior exposure to varicella and the potential for a specific immunological memory response to VZV as measured by VZV-RCF (6, 22). Exclusion criteria were as follows: immunosuppression resulting from neoplastic disease, corticosteroids or other therapy; significant underlying illness that would be expected to prevent completion of the study; any other condition (eg, extensive psoriasis, chronic pain syndrome, cognitive impairment, severe hearing loss) that in the opinion of the investigator might interfere with the required evaluations; not ambulatory; prior herpes zoster; receipt of immunizations (eg, hepatitis B vaccine, influenza vaccine) within 1 month of study entry; current depression, suicidal risk, use of mood-altering medications, or a combination of these depressive factors; any acute intercurrent illness that might interfere with interpretation of the study (such as an acute viral illness within the last 2 weeks); and unable to commit to the intervention schedule. Women were postmenopausal.

Procedures

The protocol and informed consent documents were reviewed and approved by the Institutional Review Boards at the University of California, San Diego (UCSD) and the San Diego Veterans Affairs Healthcare System. Informed consent was obtained during the initial visit. Consenting subjects were then interviewed to obtain demographic information and medical history. The Structured Clinical Interview for DSM-IV was administered to confirm that participants did not have a major depression or another major psychiatric disorder. Participants were again informed about the intervention schedule and the randomization procedures, allowing them another opportunity to reconsider participation before study entry.

Once the baseline assessments were completed, participants were randomized into the TCC or control group using a computer-generated random assignment scheme, which assigned subjects in a 1:1 ratio to each group. After random assignment to either the TCC intervention group or wait list control group, participants assigned to the wait list condition were again informed that they would be eligible to receive instruction in TCC at the end of the study.

All assessment procedures described below were identical for the two groups. Assessment of health functioning was obtained at baseline, at weeks 5, 10, and 15 during the intervention, and at 1-week postintervention. Blood samples for assay of VZV-RCF were obtained at baseline and at 1-week postintervention. At baseline and 1-week postintervention, interviews and blood sampling procedures were carried out in the General Clinical Research Center outpatient clinic at UCSD. At the 1-week postintervention assessment, eligibility criteria were again confirmed; no subjects reported a change of medical status that might have influenced interpretation of the immune measures such as the presence of an acute infectious illness within 2 weeks before blood sampling. For the assessment of health functioning during the intervention, the Medical Outcomes short form SF-36 was mailed to participants 1 week before the assessment at weeks 5, 10, and 15. On the day before the health functioning assessment was due, subjects received a telephone reminder that asked them to complete the SF-36 the next morning and return it by mail. On the day that the SF-36 was due, a second phone call was placed to confirm that the SF-36 had been completed and returned to the project coordinator. If a questionnaire had not been received within 5 days of assessment, the subject was again called to confirm that the SF-36 had been completed and returned. With the exception of the subject dropouts as noted below, these procedures yielded a >98% rate of accurate and timely completion.

At baseline and 1-week postintervention, blood sampling for VZV-RCF was obtained between 8 AM and 10 AM to control for circadian effects. Samples were obtained at the UCSD General Clinical Research Center, a site that was different from where the TCC classes were taught. A 21-gauge IV catheter was inserted into a forearm vein, and after 15 minutes of rest, 60 ml of blood was drawn for use in the VZV-RCF assay. Immune assays were conducted within 2 hours of sample acquisition by a technician blind to the subjects' intervention group assignment. To minimize the effects of interassay variability on the comparison of group differences in VZV-RCF, blood samples were collected from subjects in TCC and control groups on the same day. On average, 4 to 6 individual VZV-RCF assays were run on each assay day with 2 to 3 samples from each group.

Intervention

TCC uses "meditation through movement," incorporating elements of balance, postural alignment, and concentration. Subjects learned to perform 20 standardized movements under the guidance of an expert TCC teacher (S. Patterson, MS; 20 years experience) who conducted all treatment sessions throughout the 15-week intervention period. Although TCC is performed as slow, relaxed, continuous movements, it also requires a considerable amount of work by the leg muscles and thus has an aerobic component of moderate intensity. Thus, each TCC session was restricted to 45 minutes with a 10-minute warm-up, a 30-minute practice, and a 5-minute cool-down. Sessions were given three times per week (45 sessions over 15 weeks) and were administered during the middle of the day from 1 PM to 1:45 PM at a site in the La Jolla community that was separate from the location of the study assessments at UCSD. There were two cohorts for this intervention trial with each wave of assessments lasting 16 weeks. The first cohort included 10 TCC subjects and 10 controls who were allocated to the intervention in March; the second cohort had 8 TCC subjects and 8 controls who were allocated to the intervention in July. There were no seasonal differences in baseline VZV-RCF between the two cohorts.

Participants assigned to the wait list control group were instructed to maintain their routine activities and not to begin any new meditation, mind-body (eg, yoga), or exercise programs; adherence was confirmed by self-report. These control participants were promised a TCC program and given a voucher for instruction at the end of the study.

Outcome Measures

The two main outcomes assessed in this study were VZV-specific CMI and health functioning. VZV-specific CMI was measured by VZV-RCF; decreases in this immune parameter are thought to correlate with risk of HZ (1–4, 23). Health functioning was evaluated with the Medical Outcomes Study short form, SF-36 (24), which measures eight parameters of health status: general health perceptions (5 items); physical functioning (10 items); role limitations due to physical problems (4 items; role-physical); bodily pain (2 items); vitality (4 items); social functioning (2 items); role limitations due to emotional problems (3 items; role-emotional); and mental health (5 items) (25). As one of the most widely used instruments, the SF-36 has been found to be a useful tool in the assessment of health status in the elderly and in the measurement of burden in populations who are suffering from chronic med-

ical conditions, psychiatric conditions, or both (25–27). In older adult populations, the SF-36 shows a high internal consistency (Cronbach's alpha exceeded 0.8 for each parameter of health status) and has good discriminative validity in distinguishing between those with and without markers of poorer health (28).

VZV-specific immunity was determined by means of a VZV-RCF assay that measures the frequency of PBMC, and specifically, CD4+ CD45RO+ T cells or memory T cells in PBMCs that proliferate in response to VZV antigen (22, 23, 29–31). In older adults ($N = 200$), VZV-RCF averages about 10 responder cells per 100,000 PBMC (range, 2–64 VZV-RCF × 100,000 PBMCs) (23). Briefly, PBMCs were separated from heparinized blood using Ficoll Hypaque (density = 1.077, Sigma, St. Louis, MO) density centrifugation at room temperature. Lymphocytes were collected at the interface, washed twice with HBSS and resuspended in RPMI 1640 medium (Gibco) supplemented with penicillin (100 U/ml), streptomycin (100 μg/ml), and L-glutamine (1 mM), and with 10% autologous serum (blood collected in nonheparinized tubes was allowed to clot at room temperature for 30 minutes and serum was separated by centrifugation). PBMCs were counted with a hematocytometer using Trypan Blue staining. Cell-free VZV and control antigens prepared from VZV-infected and uninfected diploid human fibroblasts (M. Levin, University of Colorado) were diluted (1:200) in HBSS and dispensed in 10-μl aliquots to each well of 96-well U-bottom microtiter plates (Costar Product #3799). Single large batches of VZV and of control antigen were prepared and aliquoted, and the same antigen preparations were used for all assays in the study. Replicate cultures ($N = 24$) containing 50,000, 25,000, 12,000, 6250, 3125, and 1560 PBMCs/well were cultured with a 1:200 dilution of cell-free VZV antigen for 10 days, then labeled for 6 hours with 0.25 Ci of ^{3}H-thymidine (6.7 Ci/mmol, 1 mCi/ml ICN, Costa Mesa, CA) per well. Parallel control cultures were stimulated with diluted control antigen. Plates were harvested onto filtermats (LKB 1205–401) using a Skatron Instruments Micro 96 harvester, and the material from each well was counted for 5 minutes in a Wallac Betaplate 1205 Scintillation Counter. Responder wells are defined as wells with counts per minute >3 SD greater than the median counts per minute in the 24 replicate control wells containing the same number of PBMCs. RCF is interpolated from a plot of the log of the percentage of nonresponder wells against the number of PBMCs per well as the point at which 37% of VZV antigen-stimulated wells are nonresponders, according to the procedures of Hayward et al. (23). RCF is expressed as the mean number of PBMCs required to yield one VZV-specific proliferating cell (29). The coefficients of variation (as 100 × the standard deviation of the residuals/mean RCF) for intraassay replicates were 5%, whereas interassay replicates obtained over a 3- to 5-month interval were 18%, consistent with the findings of Hayward et al. (23). Due to assay variance and population variability, 12 or more subjects per group are recommended for between group comparisons (22).

Statistical Analyses

The underlying structure of the study was a randomized experiment with two interventions: TCC and wait list control. Demographic information was obtained at the baseline assessment. For evaluation of health functioning, there were assessments at baseline, every 5 weeks during the intervention, and at 1 week immediately after the end of the intervention. Thus, assessments of health functioning were taken during the intervention when classes were regularly meeting and immediately after the intervention when classes were no longer administered. For evaluation of VZV-specific immunity, measures were taken at baseline and 1-week postintervention.

Statistical analyses were based on the data set for the patients who were randomly assigned to groups and had a baseline assessment, intent-to-treat sample (TCC, $N = 18$; control, $N = 18$). For VZV-RCF, baseline values were not available in three subjects due to difficulties in blood sampling ($N = 2$) and an error in VZV-RCF assay ($N = 1$); intent-to-treat sample (TCC, $N = 17$; control, $N = 16$). All statistical analyses used intent-to-treat principles in which data from the last assessment were carried forward to all future time points.

Descriptive statistics were generated for all variables. Two sample t tests were used for the comparison of continuous variables (age, educational level, income level) and Pearson's chi-square tests were used for the comparison of categorical variables (gender, ethnicity, marital and employment status). To test the effects of TCC versus control intervention on VZV-RCF, an intervention group (TCC, control) × time (baseline, week 1 postintervention) repeated-measures analysis of variance was conducted. A simple effect of group differences at week 1 postintervention was hypothesized to show a significant difference. To test the effects of TCC versus control intervention on each of the SF-36 scores, a 2 intervention group (TCC, control) × time (5, 10, 15 weeks, week 1 postintervention) repeated analysis of covariance was used, covarying for baseline levels. Again, a simple effect of group differences at week 1 postintervention was hypothesized to reveal a significant difference, after controlling for baseline levels. Analyses were carried out for the intent-to-treat sample and for the sample who completed the study.

A further secondary hypothesis concerned whether TCC would be most effective in those older adults who had the greatest physical, emotional, and general health impairments at baseline. To test this hypothesis, exploratory analyses were conducted that were restricted to those SF-36 scores that showed group differences at week 1 postintervention. The sample was stratified into those with either high or low health functioning at baseline, and a 4 intervention group (TCC: high or low SF-36 scores at entry, control: high or low SF-36 scores at entry) × time repeated-measures analysis was used. It was hypothesized that SF-36 indices that obtained significance from the initial group by time analyses of variance would show exaggerated results for interaction contrasts. Specifically, it was hypothesized that the effect of TCC would be differentially beneficial for those above and below the median SF-36 score, allowing for more marked improvement over time only for the TCC-low baseline group.

RESULTS

A total of 116 phone calls were received from persons expressing interest in the study; project staff were able to schedule 85 persons for a phone screening interview, whereas 31 (26%) did not respond to follow-up contact, were unwilling to provide eligibility information in a phone screening, or both. Of the 85 persons who underwent phone screening, 57 individuals met preliminary entry criteria; 28 (24%) were not eligible. Among the possible participants, 21 persons (18%) declined further participation due to the study's time commitment, blood sampling, possibility of random assignment, or a combination of these factors. Thus, a total of 36 interested callers initiated the study, met eligibility criteria, and were randomly assigned to either the TCC group ($N = 18$) or the wait list control group ($N = 18$). Before the week 5 intervention assessment, four persons dropped out of the TCC group due to difficulties traveling to the intervention site three times a week, and one person dropped out of the wait list control group. The average age and SF-36 scores of those subjects who dropped out were similar to the average age and SF-36 scores of those subjects who completed the study. Baseline VZV-RCF and SF-36 data from the five dropouts were carried forward across all intervention assessments for the analyses. The level of participation in TCC during the duration of the remaining intervention period was high. Of the total possible sessions ($N = 45$), median compliance was 39, with a range of 29 to 42 sessions attended.

Features of the two groups are shown in Table 1. The two groups were similar in age, gender, ethnicity, marital status, current employment status, and educational level.

In the intent-to-treat sample, VZV-RCF increased from baseline to 1-week postintervention in the TCC intervention group [$F(1,31) = 4.4$, $p < 0.05$], whereas the wait list control

TABLE 1. Characteristics of the study population

Characteristic	Tai Chi Chih Group (n = 18)	Control Group (n = 18)	Significance
Age (years) [mean (SD)]	70.9 (6.8)	70.1 (6.0)	t (34) = −0.3; p = 0.74
Gender			
Female (%)	67	78	$\chi^2(1)=0.6, p=0.46$
Ethnicity			
Euro-American (%)	94	94	$\chi^2(1)=2.0, p=0.37$
Marital status			
Married (%)	63	71	$\chi^2(1)=1.5, p=0.47$
Employment status			
Currently employed (%)	33	36	$\chi^2(1)=2.1, p=0.56$
Education (years) [mean (SD)]	16.4 (2.8)	15.3 (2.2)	t (34) = −1.4; p = 0.17

group did not change (Figure 1). A test of a simple effect of group differences at 1-week postintervention was not statistically significant. To provide a further indication of the effects of the intervention on VZV-RCF, percentage change from baseline to postintervention was examined in individual subjects. The interassay coefficient of variation (18%) was used to define the normal range of fluctuation of VZV-RCF; percentage change values that exceeded the coefficient of variation were identified as increases or decreases, respectively. Within the TCC intervention group, 9 subjects increased, 7 were unchanged (including 4 who were analyzed as intent-to-treat cases), and 1 subject decreased; whereas in the control group, 3 subjects increased, 8 were unchanged (1 intent-to-treat case), and 5 decreased (likelihood ratio = 6.1, $p < 0.05$).

For each of the measures of health functioning, simple effects of group differences at 1-week postintervention were used to test the effects of TCC intervention versus control on SF-36 scores. In the intent-to-treat sample, no significant differences were found between the TCC and control groups at 1-week postintervention, although the TCC group tended to show higher values on SF-36 scores role-physical [$F(1,33)$ = 2.7, p = 0.10] and physical functioning ($F(1,33)$ = 1.9, p = 0.17) as compared with controls. Follow-up analyses were completed in the sample who completed the intervention (TCC, N = 14; control, N = 17), and showed that the TCC group had significantly higher scores on SF-36 role-physical scores [$F(1,28)$ = 5.1, $p < 0.05$; Figure 2] and physical functioning scores [$F(1,28)$ = 4.5, $p < 0.05$] at 1-week postintervention as compared with controls. There were no group differences at postintervention for the other SF-36 scores including general health, vitality, bodily pain, social functioning, role-emotional, and mental health. Finally, additional analyses did not reveal any correlations between VZV-RCF and baseline or postintervention SF-36 scores.

In this community-dwelling sample of older adults, health functioning was high at study entry (ie, at baseline), and 10 subjects in the TCC group and 10 subjects in the control group had scores at 100, the "ceiling" for SF-36 role-physical and physical functioning. To test the differential effects of TCC on the participants who had physical limitations as compared with those who did not, exploratory analyses were conducted in which the TCC and control groups were stratified into those who had high (N = 10) or low (N = 8) SF-36 role-physical or

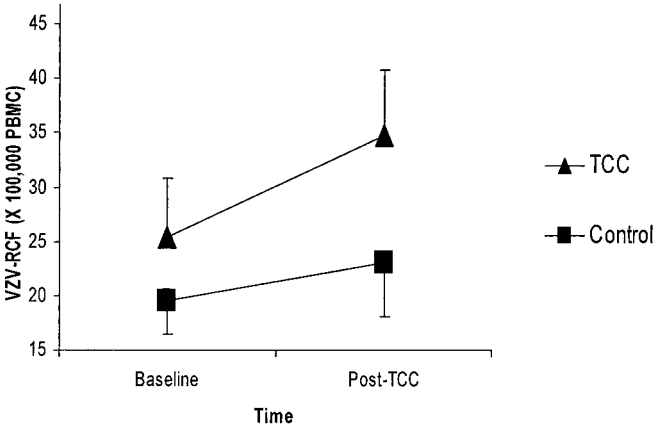

Fig. 1. VZV-specific CMI (VZV-RCF) at baseline and at 1-week postintervention in the intent-to-treat sample. VZV-RCF increased from baseline to 1-week postintervention in the TCC group [$F(1,31)$ = 4.4, $p<0.05$] but not in the control group. Data are mean ± SEM values.

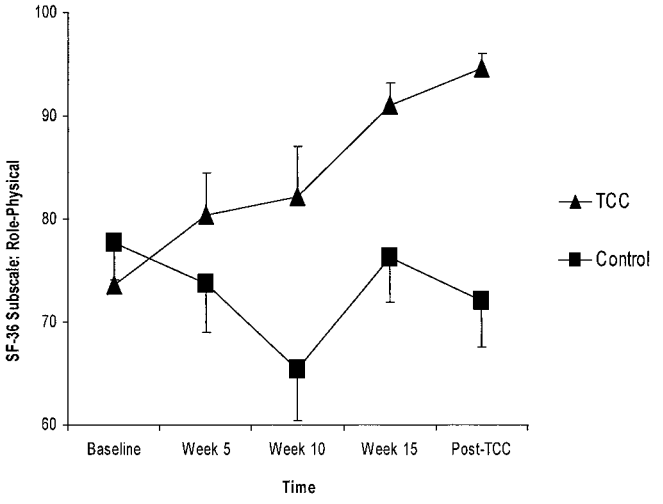

Fig. 2. SF-36 scale score role-physical at baseline, during the itnervention at weeks 5, 10, and 15, and 1-week postintervention in the completer sample, TCC (N = 14) and control group (N = 17). SF-36 role-physical scores were higher in the TCC group as compared with controls [$F(1,28)$ = 5.1] at postintervention. Data are mean ± SEM scores.

physical functioning scores at baseline. Interaction contrasts demonstrated more marked improvement over time in the TCC group who had low health functioning at baseline with significant differences for SF-36 role-physical [$F(1,32) = 12.1$, $p < 0.01$] and for physical functioning [$F(1,32) = 13.3$, $p < 0.001$] as compared with the TCC group who had no impairments of physical status.

DISCUSSION

This is the first study to demonstrate that a behavioral intervention can influence a virus-specific CMI response that is important in protection against symptomatic reinfection and in VZV reactivation. In older adults, who on average show declines in VZV-specific immunity and increases in risk for herpes zoster, VZV-RCF increased following administration of TCC for 15 weeks. In addition, TCC was associated with improvements in physical health functioning, with greatest effects in those older adults who had impairments of physical status at entry into the study. However, in light of the small sample, these findings should be cautiously interpreted and viewed as preliminary in nature.

The TCC group showed a robust increase of VZV-RCF and, on average, had a nearly 50% increase of VZV-RCF from baseline to 1-week postintervention using this intrasubject approach. However, due to the high intersubject variation of VZV-RCF, group differences were not found at 1-week postintervention; the group size only marginally exceeded the number recommended by Hayward for between-group comparisons (22).

In response to vaccination with live attenuated Oka/Merck varicella vaccine, Levin et al. have demonstrated about a 75% increase above baseline in more than 200 seropositive elderly adults (mean age 67 years) (32, 33), an increase that is similar to that induced by an episode of herpes zoster (33). Response to vaccination is sustained for months to years (34), and further research is needed to evaluate the durability of the effects of TCC on VZV-CMI. Increases of VZV-RCF are primarily driven by the response of CD4+ CD45RO+ T cells or memory T cells (31), and we speculate that TCC might have comparable effects on these cell types across the full spectrum of antigenic challenge with potential implications for multiple infectious diseases of which no vaccine is yet available (eg, HIV). Moreover, the increase of VZV-RCF in this sample is even more striking because the older adults were in good health, not depressed, and had higher baseline levels of VZV-RCF than had been previously reported in this at-risk population (23).

Assay of VZV-RCF is a relatively laborious procedure that uses a limiting dilution analysis to quantitate memory T cell responses by diluting out VZV-specific CD4+ CD45RO+ T cells in PBMC. Number of antigen presenting cells is not limiting in quantitating the responder cell frequency. In contrast to conventional antigen-stimulated proliferation in which there is no linear relationship between the number of responding cells and amount of radioactive thymidine that is incorporated, the assay of VZV-RCF is generally viewed as superior (6). Cytokine-based methods to evaluate T lymphocyte responses may also prove sensitive in evaluating VZV-CMI as VZV antigen stimulated production of interferon and interleukin-2 shows declines in older adults (35). There are, however, only limited data on the relationships of cytokine assays (eg, ELISPOT) to HZ risk (22). Alternatively, rather than using a surrogate of HZ risk as reflected by VZV-CMI, there is interest in evaluating specific viral measures. Yet, in contrast to other herpes viruses that are shed from mucosal sites several times a year for decades after primary infection (36), shedding of VZV is only detected at times of reactivation with overt clinical symptoms (37). In addition, the low annual incidence of herpes zoster (approximately 3–7 cases per 1000 persons per year in that age group) means that large numbers of subjects must be evaluated to determine the efficacy of an intervention on clinical outbreaks. For example, to test the efficacy of a varicella vaccine, the ongoing VA Cooperative Study #403: the Shingles Prevention Study enrolled >37,000 older adults to answer whether boosting VZV immunity results in a reduction in the frequency, severity, or both, of herpes zoster.

The Medical Outcomes Study short form, SF-36, is a widely validated instrument that provides a multidimensional assessment of health status. This study found that TCC was associated with improvements in physical functioning and physical role limitations, especially in those older adults who had impairments in physical status at entry. Indeed, in those older adults whose baseline scores were at or below the population norm for men and women aged 60 years and older (24), these observations are particularly striking; the TCC intervention led to increases in health functioning to levels that were at or above the population norms after its completion. Moreover, it is important to note that the magnitude of change from baseline to postintervention was large and comparable to that reported for certain medical procedures. For example, in the instance of SF-36 role-physical scores, the average change in the low TCC group was comparable or exceeded that reported for hip replacement surgery (38) or for heart valve replacement in older adults (39), although it is not known whether the effects of TCC persist in the long term.

Anecdotally, subjects in the TCC group generally reported feelings of relaxation, increased energy, and less fatigue. Future studies that use more sensitive measures than the SF-36 are needed to evaluate the effects of TCC on these various symptoms as well as other domains that are thought to be influenced by TCC such as balance, postural alignment, and concentration.

Several pathways may mediate the effects of TCC on immunity and health functioning. Although none has yet been established, interest has focused on two components, relaxation and exercise, without necessarily considering their effects in concert as occurs during the practice of TCC. In a meta-analyses on the effects of relaxation training, Hyman et al. (40) found that various relaxation response-based interventions led to a reduction of clinical somatic symptoms with additional effects on symptoms of anxiety and depression

(41), blood pressure (42), and recovery from immune-mediated diseases such as psoriasis (43). Decreases of autonomic arousal that follow relaxation-based interventions, and possibly TCC, may modulate immunity. Substantial evidence suggests that sympathetic activation has inhibitory effects on cellular immune responses in aging (44–46), whereas decreases of sympathetic outflow, adrenergic receptor antagonism, or both abrogate stress-induced immune suppression (44, 47). In addition, for individuals infected with human immunodeficiency virus, a behavioral stress management intervention decreased levels of psychosocial stress, which were coupled with decreases of cortisol and improvements of immunity as reflected by decreases of herpes simplex antibody concentrations (48). However, TCC is a multifaceted intervention that includes not only aspects of relaxation and meditation but also components of aerobic exercise. During the acute practice of TCC, for example, increases of heart rate, VO_2 consumption, and lactate accumulation are reported, indicating that TCC serves as an aerobic exercise of moderate intensity (49). Further data show that TCC training over 12 months enhances cardiorespiratory function as measured by increases of VO_2 MAX and decreases of blood pressure (19). The benefits of exercise and exercise training on immunity in the elderly have been previously reported (50, 51). Finally, we cannot exclude the possibility that the increase of VZV-RCF in the TCC intervention group was related to reactivation of VZV and increases of viral load. However, none of our TCC or control participants reported clinical symptoms of herpes zoster, nor did they report subclinical symptoms of dermatomal pain that can also be associated with boosting VZV immunity in healthy adults (6, 52).

There are several limitations to the study that need to be addressed before these data can be translated for clinical use in the elderly. First, it is unclear whether the effects of TCC on SF-36 scores and VZV-specific immunity are sustained beyond the intervention period. In contrast, immunization with investigational live attenuated varicella-zoster vaccine leads to increases in VZV-RCF that persist for years following its administration (32). Second, the sample population was limited to community dwelling older adults who were generally in good medical health. Although those participants with low scores on the SF-36 showed the most robust increases of physical functioning in response to TCC, these results may not be generalizable to patients with acute or chronic medical disorders. Third, half of the subjects in the TCC group who had SF-36 scores above the median did not respond to the trial. The absence of effect in this subgroup may be driven by a "ceiling" in the assessment of health functioning, a lack of efficacy of TCC in those older adults who show minimal impairments of health status, or a combination of these facets. In addition, the frequency of subjects who had SF-36 scores at the ceiling of the scale and the restricted range of score likely precluded detection of a relationship between measures of health status and VZV-CMI in this older adult population. Fourth, the numbers of subjects are small, particularly in those analyses concerning the effectiveness on TCC on those older adults with the greatest physical impairment. Fifth, the effects of TCC were compared with a wait list control condition, and nonspecific intervention factors, including instruction, attention, and social support during the group TCC classes, expectancy, and enthusiasm about assignment to the TCC group, could have affected the results. Finally, anticipatory or acute stress effects could have contributed to the group differences of VZV-RCF at 1-week postintervention, although these effects were likely minimized by the different times, location, and personnel for blood sampling procedures and TCC sessions.

Despite these limitations, this report represents an important step in evaluating whether behavioral interventions alter measures of immunity and health functioning in older adults. This research shows that an alternative medicine, ie, a behavioral intervention, namely, TCC, results in improvements in measures of immunity to VZV in an older adult population at risk for herpes zoster. TCC is a standardized and manualized series of exercises that can be readily administered in a group setting to older adults with cost-effectiveness. In conclusion, this study indicates that TCC has value for improving functional limitations in physical domains and for enhancing at least one clinically relevant measure of virus-specific cellular immunity.

This work was supported in part by grants AA10215, AA13239, MH55253, T32-MH18399, AG18367, AT00255, AR/AG41867, NIH grant M01 RR00827. The authors thank Dr. Jerry Bobo and Claudine Miller, MA, for assistance with subject recruitment and subject evaluation and for their dedication to the study; Susan Patterson for teaching the TCC classes; Jeff Dang, MPH, for statistical advice; Dr. Myron Levin for providing VZV and control antigen; Dr. Anthony Hayward for consultation on the VZV-RCF assay.

REFERENCES

1. Hope-Simpson RE. The nature of herpes zoster: a long-term study and a new hypothesis. Proc R Soc Med 1965;58:9.
2. Oxman MN. Immunization to reduce the frequency and severity of herpes zoster and its complications. Neurology 1995;45(suppl):41–6.
3. Straus S, Oxman MN. Varicella and herpes zoster. In: Freedberg IM, editor. Fitzpatrick's dermatology in general medicine. New York: McGraw Hill; 1999. p. 2427–50.
4. Arvin AM. Cell-mediated immunity to varicella-zoster virus. J Infect Dis 1992;166(suppl):35–41.
5. Arvin AM. Immune responses to varicella zoster virus. Philadelphia: Saunders; 1996.
6. Levin MJ, Hayward AR. Prevention of herpes zoster. Infectious Dis Clin North Am 1996;10:657–75.
7. Murasko DM, Nelson BJ, Matour D, Goonewardene IM, Kaye D. Heterogeneity of changes in lymphoproliferative ability with increasing age. Exp Gerontol 1991;26:269–79.
8. Schmader KE, Studenski S, MacMillan J, Grufferman S, Cohen HJ. Are stressful life events risk factors for herpes zoster? Am J Geriatr Soc 1990;38:1188–95.
9. Irwin M, Costlow C, Williams H, Artin KH, Chan CY, Stinson DL, Levin MJ, Hayward AR, Oxman MN. Cellular immunity to varicella-zoster virus in patients with major depression. J Infect Dis 1998;178(suppl):104–8.
10. Miller GE, Cohen S. Psychological interventions and the immune system: a meta-analytic review and critique. Health Psychol 2001;20:47–63.
11. Smyth JM, Stone AA, Hurewitz A, Kaell A. Effects of writing about stressful experiences on symptom reduction in patients with asthma or rheumatoid arthritis: a randomized trial [see comments]. JAMA 1999; 281:1304–9.
12. Petrie KJ, Booth RJ, Pennebaker JW, Davison KP, Thomas MG. Disclo-

sure of trauma and immune response to a Hepatitis B vaccination program. J Consult Clin Psychol 1995;63:787–92.
13. Fawzy FI, Fawzy NW, Hyun CS, Elashoff R, Guthrie D, Fahey JL, Morton DL. Malignant melanoma: effects of an early structured psychiatric intervention, coping, and affective state on recurrence and survival 6 years later. Arch Gen Psychiatry 1993;50:681–9.
14. Fawzy FI, Kemeny ME, Fawzy NW, Elashoff R, Morton D, Cousins N, Fahey JL. A structured psychiatric intervention for cancer patients: II. Changes over time in immunological measures. Arch Gen Psychiatry 1990;47:729–35.
15. Kiecolt-Glaser JK, Glaser R, Williger D, Stout J, Messick G, Sheppard S, Ricker D, Romisher S, Briner W, Bonnell G, Donnerberg R. Psychosocial enhancement of immunocompetence in a geriatric population. Health Psychol 1985;4:25–41.
16. Li JX, Hong Y, Chan KM. Tai chi: physiological characteristics and beneficial effects on health. Br J Sports Med 2001;35:148–56.
17. Wolf SL, Sattin RW, O'Grady M, Freret N, Ricci L, Greenspan AI, Xu T, Kutner M. A study design to investigate the effect of intense Tai Chi in reducing falls among older adults transitioning to frailty. Control Clin Trials 2001;22:689–704.
18. Wolf SL, Barnhart HX, Kutner NG, McNeely E, Coogler C, Xu T. Reducing frailty and falls in older persons: an investigation of Tai Chi and computerized balance training. Atlanta FICSIT Group. Frailty and Injuries: Cooperative Studies of Intervention Techniques J Am Geriatr Soc 1996;44:489–97.
19. Lan C, Lai JS, Chen SY, Wong MK. 12-month Tai Chi training in the elderly: its effect on health fitness. Med Sci Sports Exerc 1998;30: 345–51.
20. Lan C, Chen SY, Lai JS, Wong MK. The effect of Tai Chi on cardiorespiratory function in patients with coronary artery bypass surgery. Med Sci Sports Exerc 1999;31:634–8.
21. Li F, Harmer P, McAuley E, Duncan TE, Duncan SC, Chaumeton N, Fisher KJ. An evaluation of the effects of Tai Chi exercise on physical function among older persons: a randomized controlled trial. Ann Behav Med 2001;23:139–46.
22. Hayward AR. In vitro measurement of human T cell responses to varicella zoster virus antigen. Arch Virol Suppl 2001;143–9.
23. Hayward AR, Zerbe GO, Levin MJ. Clinical application of responder cell frequency estimates with four years of follow up. J Immunol Meth 1994;170:27–36.
24. Ware JE. SF-36 Health Survey manual and interpretation guide. Boston: Nimrod; 1993.
25. McHorney CA. Measuring and monitoring general health status in elderly persons: practical and methodological issues in using the SF-36 health survey. Gerontologist 1996;36:571–83.
26. McHorney CA, Ware JE, Lu JFR, Sherbourne CD. The MOS 36 item Short Form Health Survey (SF-36): III. Tests of data quality, scaling assumption, and reliability across diverse patient groups. Med Care 1994;32:40–6.
27. Beusterien KM, Steinwald B, Ware JE. Usefulness of the SF-36 Health Survey in measuring health outcomes in the depressed elderly. J Geriatr Psychiatr Neurol 1996;9:13–21.
28. Lyons RA, Perry HM, Littlepage BNC. Evidence for the validity of the Short-form 36 Questionnaire (SF-36) in an elderly population. Age Ageing 1994;23:182–4.
29. Hayward A, Levin M, Wolf W, Angelova G, Gilden D. Varicella-zoster virus-specific immunity after herpes zoster. J Infect Dis 1991;163:873–5.
30. Hayward AR, Herberger M. Lymphocyte responses to varicella zoster virus in the elderly. J Clin Immunol 1987;7:174–8.
31. Chinn A, Cosyns M, Hayward AR. T cell proliferative response to interleukin 2: different frequency of responders among CD45R0 and CD45RA subsets. Cell Immunol 1990;131:132–9.
32. Levin MJ, Murray M, Zerbe GO. Immune responses of elderly persons 4 years after receiving a live-attenuated varicella vaccine. J Infect Dis 1994;170:522–6.
33. Levin MJ, Murray M, Rotbart HA, Zerbe GO, White CJ, Hayward AR. Immune response of elderly individuals to a live-attenuated varicella vaccine. J Infect Dis 1992;166:253–9.
34. Levin MJ, Ellison MC, Zerbe GO, Barber D, Chan C, Stinson D, Jones M, Hayward AR. Comparison of a live attenuated and an inactivated varicella vaccine to boost the varicella-specific immune response in seropositive people 55 years of age and older. Vaccine 2000;18:2915–20.
35. Asanuma H, Sharp M, Maecker HT, Maino VC, Arvin AM. Frequencies of memory T cells specific for varicella-zoster virus, herpes simplex virus, and cytomegalovirus by intracellular detection of cytokine expression. J Infect Dis 2000;181:859–66.
36. Wald A, Corey L, Cone R, Hobson A, Davis G, Zeh J. Frequent genital herpes simplex virus 2 shedding in immunocompetent women: effect of acyclovir treatment. J Clin Invest 1997;99:1092–7.
37. Zaal MJ, Volker-Dieben HJ, Wienesen M, D'Amaro J, Kijlstra A. Longitudinal analysis of varicella-zoster virus DNA on the ocular surface associated with herpes zoster ophthalmicus. Am J Ophthalmol 2001;131: 25–9.
38. Katz JN, Larson MG, Phillips CB, Fossel AH, Liang MH. Comparative measurement sensitivity of short and longer health status instruments. Med Care 1992;30:917–25.
39. Phillips RC, Lansky DJ. Outcomes management in heart valve replacement surgery: early experience. J Heart Valve Dis 1992;1:42–50.
40. Hyman RB, Feldman HR, Harris RB, Levin RF, Malloy GB. The effects of relaxation training on clinical symptoms: a meta-analysis. Nurs Res 1989;38:216–20.
41. Kabat-Zinn J, Massion AO, Kristeller J, Peterson LG, Fletcher KE, Pbert L, Lenderking WR, Santorelli SF. Effectiveness of a meditation-based stress reduction program in the treatment of anxiety disorders. Am J Psychiatry 1992;49:936–43.
42. Alexander CN, Schneider RH, Staggers F, Sheppard W, Clayborne BM, Rainforth M, Salerno J, Kondwani K, Smith S, Walton KG, Egan B. Trial of stress reduction for hypertension in older African Americans: II. Sex and risk subgroup analysis. Hypertension 1996;28:228–37.
43. Kabat-Zinn J, Wheeler E, Light T, Skillings A, Scharf MJ, Cropley TG, Hosmer D, Bernhard JD. Influence of a mindfulness meditation-based stress reduction intervention on rates of skin clearing in patients with moderate to severe psoriasis undergoing phototherapy (UVB) and photochemotherapy (PUVA). Psychosom Med 1998;60:625–32.
44. Friedman EM, Irwin MR. Modulation of immune cell function by the autonomic nervous system. Pharmacol Ther 1997;74:27–38.
45. Irwin M, Brown M, Patterson T, Hauger R, Mascovich A, Grant I. Neuropeptide Y and natural killer cell activity: findings in depression and Alzheimer caregiver stress. FASEB J 1991;5:3100–7.
46. Irwin M, Hauger R, Brown M. Central corticotropin releasing hormone activates the sympathetic nervous system and reduces immune function: increased responsivity of the aged rat. Endocrinology 1992;131:1047–53.
47. Murray DR, Irwin M, Rearden CA, Ziegler M, Motulsky H, Maisel AS. Sympathetic and immune interactions during dynamic exercise: mediation via β2-adrenergic dependent mechanism. Circulation 1992;83: 203–13.
48. Cruess S, Antoni M, Cruess D, Fletcher MA, Ironson G, Kumar M, Lutgendorf S, Hayes A, Klimas N, Schneiderman N. Reductions in herpes simplex virus type 2 antibody titers after cognitive behavioral stress management and relationships with neuroendocrine function, relaxation skills, and social support in HIV-positive men. Psychosom Med 2000;62:828–37.
49. Lan C, Chen SY, Lai JS, Wong MK. Heart rate responses and oxygen consumption during Tai Chi Chuan practice. Am J Chin Med 2001;29: 403–10.
50. Nieman DC, Nehlsen-Cannarella SL, Markoff PA, Balk-Lamberton AJ, Yang H, Chritton DBW, Lee JW, Arabatzis K. The effects of moderate exercise training on natural killer cells and acute upper respiratory tract infections. Int J Sports Med 1990;11:467–73.
51. Nieman DC. Exercise immunology: future directions for research related to athletes, nutrition, and the elderly. Int J Sports Med 2000;21(suppl): 61–8.
52. Gilden DH, Wright RR, Schneck SA, Gwaltney JM Jr, Mahalingam R. Zoster sine herpete, a clinical variant. Ann Neurol 1994;35:530–3.