Clinical Infectious Diseases Advance Access published February 13, 2013

MAJOR ARTICLE

Varicella Zoster Virus–Specific Immune Responses to a Herpes Zoster Vaccine in Elderly Recipients With Major Depression and the Impact of Antidepressant Medications

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Background. The Depression Substudy of the Shingles Prevention Study (SPS) was designed to evaluate the association between major depression and immune responses to a high-titer live attenuated varicella zoster virus (VZV) vaccine (zoster vaccine), which boosts cell-mediated immunity (CMI) to VZV and decreases the incidence and severity of herpes zoster (HZ). The Depression Substudy was a 2-year longitudinal cohort study in 92 community-dwelling adults ≥60 years of age who were enrolled in the SPS, a large, double-blind, placebo-controlled Veterans Affairs Cooperative zoster vaccine efficacy study.

Methods. Forty subjects with major depressive disorder, stratified by use of antidepressant medications, and 52 age- and sex-matched controls with no history of depression or other mental illness had their VZV-CMI measured prior to vaccination with zoster vaccine or placebo and at 6 weeks, 1 year, and 2 years postvaccination.

Results. Depressed subjects who were not treated with antidepressant medications had lower levels of VZV-CMI following administration of zoster vaccine than nondepressed controls or depressed subjects receiving antidepressants even when antidepressant medications failed to alter depressive symptom severity ($P < .005$). Similar results were obtained taking into account the time-varying status of depression and use of antidepressant medications, as well as changes in depressive symptoms, during the postvaccination period.

Conclusions. Depressed patients have diminished VZV-CMI responses to zoster vaccine, and treatment with antidepressant medication is associated with normalization of these responses. Because higher levels of VZV-CMI correlate with lower risk and severity of HZ, untreated depression may increase the risk and severity of HZ and reduce the efficacy of zoster vaccine.

Keywords. herpes zoster; cellular immunity; major depression; elderly; varicella zoster virus.

Herpes zoster (HZ), commonly known as shingles is a painful neurocutaneous syndrome caused by reactivation and replication of varicella zoster virus (VZV) that has remained latent in sensory neurons following varicella infection [1–3]. VZV-specific T-cell–mediated immunity (VZV-CMI) is thought to play a critical role in protecting against HZ [4, 5]. The incidence and severity of HZ increase in association with a progressive age-related decline in VZV-CMI [6–8]. In the United States, the incidence of HZ exceeds 1% per year in persons ≥60 years of age; more than a million new cases occur each year; and one-third of the population

Received 29 September 2012; accepted 17 December 2012.

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Clinical Infectious Diseases

DOI: 10.1093/cid/cis1208

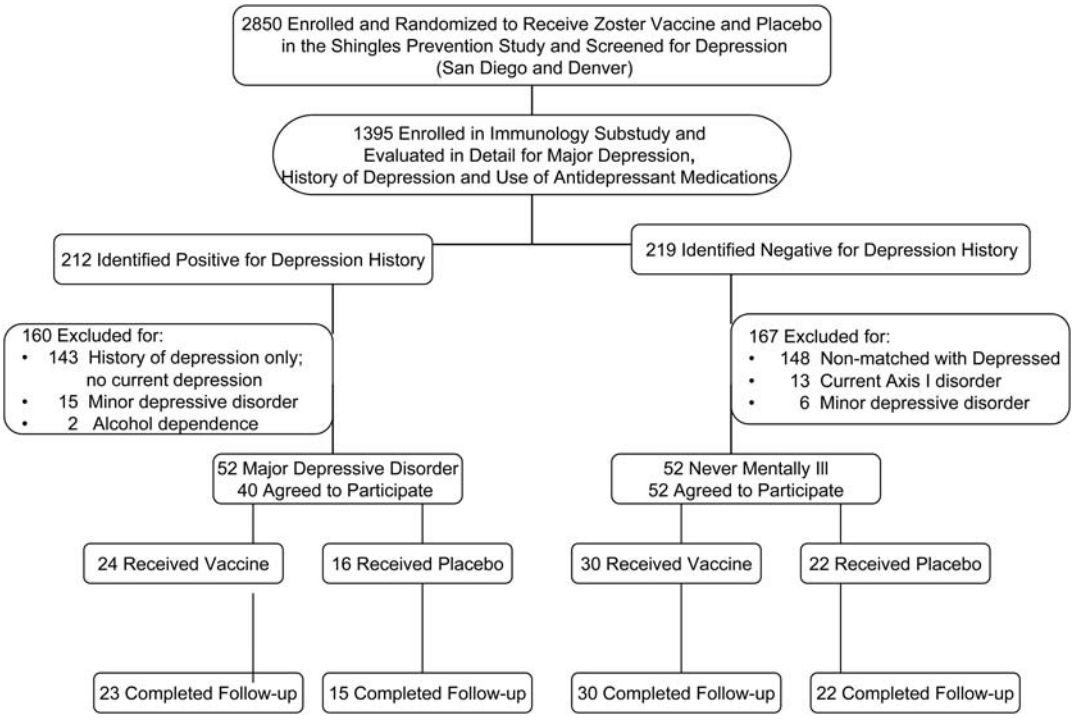

Figure 1. Consolidated Standards of Reporting Trials flow diagram of subject entry and evaluation.

is expected to suffer HZ during their lifetime—numbers destined to increase with the increasing age of the population [4, 8, 9]. The magnitude of the boost in VZV-CMI induced by zoster vaccine is correlated with vaccine efficacy observed during the Department of Veterans Affairs (VA) Cooperative Study 403: the Shingles Prevention Study (SPS) [5, 10–12].

Risk factors for HZ other than increasing age and low levels of VZV-CMI have not been clearly identified [8]. In a cross-sectional study, lower baseline levels of VZV-CMI were observed in older adults with major depression than in non-depressed controls, as evidenced by reduced numbers of VZV-specific memory T cells measured with a VZV-specific responder cell frequency (VZV-RCF) assay [13]. Furthermore, baseline VZV-CMI was higher in depressed subjects receiving antidepressants than in untreated depressed subjects, despite the failure of those medications to reduce depressive symptom severity [13]. Other studies have implicated psychological stress as a risk factor for HZ, although VZV-CMI was not evaluated [14, 15]. Because depression is common in older adults, carries significant risk for all-cause morbidity and mortality, and is often refractory to treatment [16], we investigated the association between major depression, VZV-CMI at baseline, and VZV-CMI responses to zoster vaccine. We also evaluated the effect of antidepressant medications on VZV-CMI responses.

METHODS

Subject Population and Study Design

The SPS, which provided data presented here, was a 22-site, randomized, double-blind, placebo-controlled efficacy trial of an investigational live attenuated Oka/Merck zoster vaccine in 38 546 subjects ≥60 years of age [11].

All subjects were latently infected with VZV as verified by detection of antibodies to VZV [11, 12]. SPS inclusion and exclusion criteria have been described previously [11, 13]. Subjects were randomized to receive zoster vaccine or placebo on SPS enrollment. A total of 2850 subjects, who volunteered to participate in the SPS at the Denver, Colorado, and San Diego, California, study sites between February 2000 and September 2001 also volunteered to undergo depression screening by completing an abbreviated version of the Center for Epidemiologic Studies Depression Scale (CES-D) [17] and answering 2 questions about prior episodes of depression and/or treatment for depression (Figure 1). A subset of 1395 of these screened subjects also volunteered to participate in the SPS Immunology Substudy, involving measurement of VZV-CMI and VZV antibody before vaccine or placebo administration, and 6 weeks, 1 year, and 2 years thereafter. Once enrolled in the Immunology Substudy, subjects who had screened positive

Table 1. Demographic Characteristics, Chronic Disease Score, and Severity of Depressive Symptoms in Depressed Patients and Controls

	Depressed Patients				Nondepressed Controls			
	No Antidepressant Medication		Antidepressant Medication		No Antidepressant Medication			
	n = 18		n = 22		n = 52		Significance	
	Mean	SD	Mean	SD	Mean	SD	F(2, 89)	*P* Value
Age	68.1	5.9	67.9	5.4	68.4	6.1	0.1	.94
Chronic Disease Score	1.5	1.6	2.7	2.9	2.0	2.2	1.4	.26
Beck Depression Inventory	15.9	6.6	16.5	8.7	2.7	2.5	69.1[a]	.001
Pittsburgh Sleep Quality Index	8.9	3.2	9.7	4.1	3.6	2.9	72.3[a]	.001
	%		%		%		χ^2	*P* Value
Sex (female)	66.7		45.5		59.6		2.02	.37
Ethnicity (Euro-American)	94.4		95.5		92.3		0.29	.87
Education (college degree)	44.4		31.8		50.0		2.07	.36
Marital status (married)	50.0		45.5		61.5		1.89	.39
Employment (employed)	38.9		36.4		42.3		0.24	.89

Abbreviation: SD, standard deviation.

[a] Depressed groups different from controls; depressed groups not different (*P* = .73)

for depression and/or history of depression were enrolled in the Depression Substudy. In addition, for each depressed subject, another sex- and age (± 3 years)–matched subject free of depression and history of depression was enrolled as a nondepressed control [13]. Clinical and psychiatric assessments were then completed on all Depression Substudy subjects.

Of the 212 persons fulfilling screening criteria for depression or history of depression, Structured Clinical Interview for DSM-IV (*Diagnostic and Statistical Manual of Mental Disorders*, *Fourth Edition*; SCID-DSM-IV) interview data resulted in the exclusion of 160 participants: 2 for current alcohol dependence, 15 for current depression not otherwise specified (ie, minor depressive disorder), and 143 for a history of depression who were not currently depressed. Thus, 52 subjects who had current major depression were included in the baseline assessment of immunity [13]. Forty of these 52 depressed subjects, all randomly assigned to receive zoster vaccine or placebo when they enrolled in the SPS, entered the Depression Substudy longitudinal follow-up.

Of the 219 nondepressed controls, the SCID-DSM-IV interview excluded 13 with a past history of an axis I disorder (eg, alcohol dependence) and 6 with depression not otherwise specified. Fifty-two of these 200 older adults who had never been mentally ill were selected as controls in the Depression Substudy, with age (±3 years), sex, and Chronic Disease Score (CDS) [18] chosen as matching criteria because of their known effects on cellular immune responses. These and all other Depression Substudy procedures and evaluations were carried out without knowledge of whether the subjects had received zoster vaccine or placebo, because blinded randomization occurred on SPS enrollment.

All subjects provided signed informed consent before they enrolled in the SPS, the SPS Immunology Substudy, and the Depression Substudy. These studies were approved by the Colorado Multiple Institutional Review Board (IRB) and the IRBs of the University of California, San Diego and the University of California, Los Angeles.

Clinical and Psychiatric Assessment

Procedures for evaluating eligibility and for administering the SCID-DSM-IV [19], CDS [18], Beck Depression Inventory (BDI) [20], and Pittsburgh Sleep Quality Index (PSQI) [21] have been previously described [13].

Intervention

SPS screening, randomization, and vaccination procedures were previously described [11]. On enrollment, each SPS subject received 1 subcutaneous injection of zoster vaccine or placebo in a randomized double-blind design [11].

Follow-up

Depression Substudy subjects were actively followed monthly as SPS participants, and also completed clinical and psychiatric evaluations at 6, 52, and 104 weeks postenrollment [13]. These procedures yielded a follow-up rate of 95% of the

depressed patients and 100% of the controls over the 2-year study period.

Immunologic Assessments

At each visit, samples of venous blood were obtained between 8:00 AM and 10:00 AM on the day when the clinical and psychiatric evaluations were performed. VZV-CMI was measured by VZV-RCF and interferon-γ enzyme-linked immunospot assay (ELISPOT) [22, 23]. VZV-RCF assays were performed within 2 hours after sample collection, and aliquots of the same peripheral blood mononuclear cells (PBMCs) were cryopreserved, shipped on dry ice, and assayed by interferon-γ ELISPOT as previously described [5, 13]. VZV antibodies were measured with an enzyme-linked immunosorbent assay using affinity-purified VZV glycoproteins (gpELISA) [24].

Statistical Analyses

Analyses were performed with IBM SPSS software for Windows, version 19. Distribution of VZV-RCF, ELISPOT, and gpELISA data was skewed; thus, these analyses employed natural log transformations. Differences between depressed and nondepressed subjects in background variables were evaluated using t tests or χ^2 tests. Mixed-models analysis of covariance (ANCOVA) was used to test the independent association between depression diagnosis stratified by use of antidepressant medications and VZV-specific immunity, controlling for significant covariates: age, sex, and CDS ($P < .10$). Among vaccine recipients, mixed-models ANCOVA tested changes in VZV immunity between groups over time.

RESULTS

Subject Characteristics

Figure 1 shows the flow of subject in the Depression Substudy. Controls and depressed subjects were similar in demographic and background characteristics (Table 1). Common medications included diuretics, beta-blockers, statins, and oral hypoglycemic medications. Severity of depressive symptoms and sleep disturbance was significantly higher in depressed subjects than in controls, but were comparable in depressed subjects who were or were not receiving antidepressant medications. As compared to the entire Immunology Substudy sample (N = 1395), the nondepressed controls (n = 52) were similar in age (68.4 ± 6.1 years vs 68.5 ± 6.1 years; $P = .91$), but were more likely to be female (59.6% vs 43.9% male; $P < .05$) and nonwhite (92.3% vs 97.3% white; $P < .05$), owing to higher prevalence of depression in females and the demographic characteristics of the matched depressed subjects.

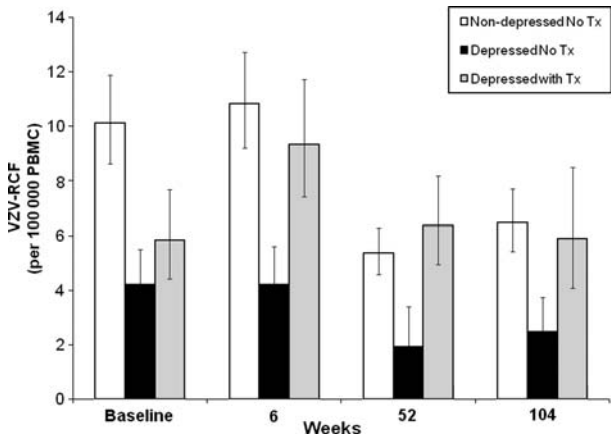

Figure 2. Bar graph of Depression Substudy varicella zoster virus–specific responder cell frequency (VZV-RCF) results at baseline and 6, 52, and 104 weeks in the 3 groups of vaccine recipients: nondepressed controls (Non-depressed No Rx; n = 30); depressed patients who are not treated with antidepressant medications (Depressed No Rx; n = 12); and depressed patients who are being treated with antidepressant medication (Depressed with Rx; n = 12). Results of the baseline VZV-RCF have been previously published [13] and are shown here for comparison with levels of VZV-RCF at 6, 52, and 104 weeks. There were significant differences at all time points between the "Depressed No Rx" and "Depressed with Rx" participants, but not between the "Depressed with Rx" and the "Non-depressed No Rx" participants (F = 6.2; $P < .005$; analysis of covariance). Abbreviations: PBMC, peripheral blood mononuclear cell; Tx, treatment; VZV-RCF, varicella zoster virus–specific responder cell frequency.

Depression and Response to Zoster Vaccine

To evaluate the effects of depression on VZV-specific immune responses in zoster vaccine recipients, we compared responses of subjects with depression with those of nondepressed controls, and stratified the depressed subjects by their use of antidepressant medications. Depressed subjects were stratified at baseline and retained group assignments during the 2 years of follow-up. Accounting for the effects of age, sex, and medical comorbidity (ie, CDS), ANCOVA showed that depressed subjects who were not using antidepressants had substantially lower levels of VZV-RCF than nondepressed controls at baseline and at all 3 time points postvaccination ($P < .005$; Figure 2 and Table 2). In contrast, depressed subjects receiving antidepressants had substantially higher levels of VZV-RCF following zoster vaccine than those of unmedicated depressed subjects ($P < .01$), and showed increases from baseline to 6 weeks postvaccination ($P < .07$), reaching levels at 6 weeks postvaccination similar to those of nondepressed controls ($P > .1$; Figure 2 and Table 2). In depressed subjects not receiving antidepressants, VZV-RCF did not change from baseline to 6 weeks postvaccination ($P = .86$), even though they had the lowest levels of VZV-RCF at baseline. Although their absolute level of VZV-RCF at 6 weeks postvaccination was

Table 2. Varicella Zoster Virus–Specific Immunity Pre– and Post–Zoster Vaccine in Vaccine Recipients Categorized at Baseline Into Groups of Depressed Subjects and Nondepressed Controls

	Depressed Patients				Nondepressed Controls			
	No Antidepressant Medication		Antidepressant Medication		No Antidepressant Medication			
	n = 12		n = 12		n = 30		Significance[a]	
	Mean	SD	Mean	SD	Mean	SD	F	*P* Value
VZV-RCF (log)							(2, 110.7) = 6.2	.005
Baseline	0.62	0.40	0.78	0.54	1.01	0.28		
6-wk	0.65	0.51	1.02	0.50	1.03	0.31		
1 y	0.60	0.46	0.86	0.37	0.76	0.34		
2 y	0.52	0.39	0.67	0.44	0.84	0.41		
ELISPOT (log)							(2, 81.7) = 2.3	.10
Baseline	1.32	0.85	1.66	0.53	1.58	0.80		
6-wk	1.72	0.74	1.90	0.54	1.82	0.91		
1 y	1.76	0.70	2.19	0.36	1.98	0.65		
2 y	1.74	0.62	1.99	0.34	1.98	0.48		
gpELISA (log)							(2, 82.4) = 0.1	.85
Baseline	2.49	0.43	2.48	0.51	2.32	0.40		
6-wk	2.63	0.47	2.73	0.45	2.68	0.43		
1 y	2.57	0.45	2.53	0.37	2.56	0.40		
2 y	2.51	0.54	2.46	0.48	2.46	0.38		

Abbreviations: ELISPOT, enzyme-linked immunosorbent spot assay; gpELISA, enzyme-linked immunosorbent assay using affinity-purified varicella zoster virus glycoproteins; SD, standard deviation; VZV-RCF, varicella zoster virus–specific responder cell frequency.

[a] Overall group × time effect.

marginally higher than that of the depressed subjects receiving antidepressants, the nondepressed controls developed a very small increase in their level of VZV-RCF following administration of zoster vaccine. This unexpected observation is explained by the fact that the nondepressed controls had high levels of VZV-RCF at baseline, comparable to those of subjects in the upper quartile of the entire Depression Substudy population of nondepressed controls (see below and Figure 3). Nevertheless, when the percentage of increase in VZV-RCF was calculated [12], significant increases were found in nondepressed controls (95% confidence interval [CI], 69.7%, 31.4%–119.2%) and in depressed subjects receiving antidepressants (95% CI, 288.1%, 90.9%–689.0%), but not in depressed subjects not receiving antidepressants (95% CI, −32.9%, −65.5% to 29.7%). No statistically significant group differences in interferon-γ ELISPOT and gpELISA responses were observed (Table 2). Among placebo recipients, baseline levels of VZV-CMI were marginally lower in depressed subjects not taking antidepressant medications compared to the other groups ($P < .07$), and there was no change in VZV-CMI over time (data not shown).

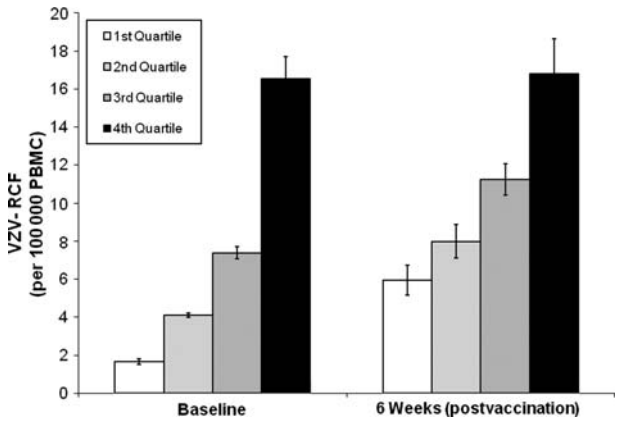

Figure 3. Varicella zoster virus–specific responder cell frequency (VZV-RCF) results stratified by quartiles at baseline and 6 weeks after zoster vaccination in the 101 vaccine recipients of the control population. 1st quartile = those with the lowest baseline levels of VZV-RCF; 4th quartile = those with the highest baseline levels of VZV-RCF. Abbreviations: PBMC, peripheral blood mononuclear cell; VZV-RCF, varicella zoster virus–specific responder cell frequency.

Table 3. Varicella Zoster Virus–Specific Immunity Pre– and Post–Zoster Vaccine in Vaccine Recipients Categorized Into Time-Varying Groups of Currently Depressed Subjects and Currently Nondepressed Comparison Group

	Currently Depressed				Currently Nondepressed			
	No Antidepressant Medication		Antidepressant Medication		No Antidepressant Medication		Significance[a]	
	Mean	SD	Mean	SD	Mean	SD	F	*P* Value
VZV-RCF (log)								
Baseline	0.62	0.40	0.78	0.54	1.01	0.28	(3, 226.5) = 4.4	.02
6 wk	0.60	0.54	0.98	0.48	1.03	0.31		
52 wk	0.28	0.83	0.89	0.27	0.74	0.35		
104 wk	0.40	0.51	0.70	0.42	0.79	0.41		
ELISPOT (log)							(3, 282.0) = 3.9	.03
Baseline	1.32	0.85	1.66	0.53	1.58	0.80		
6-wk	1.59	0.83	1.94	0.49	1.82	0.91		
52 wk	1.33	0.49	2.06	0.65	1.95	0.68		
104 wk	1.42	0.80	2.07	0.25	1.97	0.47		
gpELISA (log)							(3, 262.2) = 0.9	.91
Baseline	2.49	0.43	2.48	0.51	2.32	0.40		
6 wk	2.58	0.54	2.73	0.42	2.68	0.43		
52 wk	2.61	0.63	2.49	0.35	2.50	0.58		
104 wk	2.65	0.74	2.33	0.37	2.47	0.41		

Abbreviations: ELISPOT, enzyme-linked immunosorbent spot assay; gpELISA, enzyme-linked immunosorbent assay using affinity-purified varicella zoster virus glycoproteins; SD, standard deviation; VZV-RCF, varicella zoster virus–specific responder cell frequency.

[a] Overall group × time effect.

In the SPS Immunology Substudy, subjects with a high level of VZV-RCF at baseline (ie, those in the upper quartile, with >12 responder cells/10^5 PBMCs) showed only a very small increase in their absolute response to zoster vaccine (approximately 0.1 responder cell/10^5 PBMCs) measured 6 weeks after vaccination, whereas the 663 zoster vaccine recipients in the lower 3 quartiles (with baseline VZV-RCF from ≥3.5 to <12 responder cells/10^5 PBMCs) showed an average absolute response to zoster vaccine at 6 weeks postvaccination of 3.7–3.8 responder cells/10^5 PBMCs (unpublished data; J.H.Z., G.J., M.J.L., M.N. O.). We therefore evaluated the response among zoster vaccine recipients in the entire control sample of the Depression Substudy (N = 101 vaccine recipients) stratified in quartiles on the basis of their baseline levels of VZV-RCF. We observed that persons in the upper quartile showed a minimal increase in VZV-RCF in responses to zoster vaccine, whereas those in the lower 3 quartiles showed substantial increases in VZV-RCF from baseline to 6 weeks postvaccination (Figure 3).

Time-Varying Status of Depression and Antidepressant Use: Effect on Responses to Zoster Vaccine

Over the postvaccination follow-up period, status of depression and use of antidepressant medications varied. Hence, additional analyses were conducted to evaluate the time-varying effects of current depression and/or antidepressant use on VZV-CMI responses to zoster vaccine. For example, if a depressed subject was depressed at 6 weeks but clinically remitted at 52 weeks, that person would be classified in the analyses as depressed at 6 weeks and nondepressed at 52 weeks. Because all subjects who were using antidepressants also fulfilled criteria for major depressive disorder at time of assessment and none of the nondepressed subjects used antidepressants at any time point, only 3 groups were defined: nondepressed, currently depressed not taking antidepressant medications, and currently depressed taking antidepressant medications. This analysis reinforced the findings in Table 2; the depressed group not taking antidepressants had lower levels of VZV-RCF than the other 2 comparator groups ($P = .02$; Table 3), which was also true for their ELISPOT values ($P < .03$; Table 3). Again, no group differences were found for gpELISA responses.

To evaluate whether change in depressive symptoms severity or sleep disturbance might account for differences in VZV-RCF, severity of depressive symptoms and sleep disturbance were compared in the nondepressed and the 2 depressed groups across the pre- and postvaccination period. Whereas

nondepressed subjects had significantly lower severity of depressive symptoms and sleep disturbance compared to the 2 depressed groups (mean BDI scores over all time points: 3.4 vs 14.5 and 15.4, $P < .001$; mean PSQI scores over all time points: 3.8 vs 8.8 and 8.5, $P < .001$), the depressed group taking antidepressants and the depressed group not taking antidepressants did not differ in severity of depressive symptoms by time ($P = .27$) or severity of sleep disturbance by time ($P = .89$). In addition, the 2 depressed groups (irrespective of antidepressant use) showed similar severity of depressive symptoms and sleep disturbance (BDI overall time effect $P = .57$, for any time point, all $P > 0.40$; PSQI overall time effect $P = .15$, for any time point all $P > 0.45$). Severity of depressive symptoms or sleep disturbance was not associated with differences in VZV-RCF or ELISPOT titers at any time point (all $P > 0.4$).

DISCUSSION

Administration of zoster vaccine boosts VZV-CMI and decreases the incidence and severity of HZ in older adults [5, 11, 12]. In the Depression Substudy, zoster vaccine failed to boost VZV-CMI measured by VZV-RCF in elderly subjects with untreated major depression, even though this group had the lowest level of VZV-RCF at baseline. Among depressed subjects who were not receiving antidepressant medications, levels of VZV-RCF were low at baseline and remained low over 2 years following administration of zoster vaccine. In contrast, zoster vaccine increased levels of VZV-RCF in elderly depressed subjects treated with antidepressants, yielding levels of VZV-CMI similar to those observed in nondepressed controls. Importantly, among depressed subjects receiving antidepressant medications, the time-varying analyses showed that vaccine boosted both VZV-RCF and VZV-specific ELISPOT responses as long as treatment continued, despite the fact that treatment did not decrease depressive symptom severity. Differences in depressive symptom severity or sleep disturbance did not account for the different VZV-CMI response to zoster vaccine among the depressed subjects who were and were not receiving antidepressants.

The findings that baseline VZV-CMI and VZV-CMI responses to zoster vaccine were substantially lower in elderly individuals with untreated depression compared to age- and sex-matched nondepressed controls and to depressed subjects receiving antidepressants have important public health implications. Because the incidence and severity of HZ and its complications, particularly postherpetic neuralgia, are increased in persons with depressed VZV-CMI [5, 12], persons with untreated depression may be at greater risk for HZ and its complications than either nondepressed adults of similar age, sex, and medical comorbidity or depressed persons receiving antidepressants. Moreover, elderly persons with untreated depression appear to respond poorly to zoster vaccine and may thus be poorly protected by vaccination, at least when zoster vaccine is used as currently recommended [4]. Further research to evaluate the possible relationship between untreated depression and the risk of HZ will require a large number of subjects because of the relatively low annual incidence of HZ (approximately 10–12 cases per 1000 persons per year in persons ≥60 years of age [11]). It will also be important to determine the mechanism(s) responsible for the reduction in VZV-CMI at baseline and in response to zoster vaccine in older persons with untreated depression, and the basis for the reversal of that reduction by antidepressants, despite their failure to significantly reduce depressive symptom severity.

The finding that untreated depression is associated with reduced baseline levels of VZV-RCF [13], as well as a failure to respond to zoster vaccine, may have implications for the risk of other infectious diseases. Because VZV–RCF measures primarily VZV-specific memory T cells (CD41 CD45RO1 T cells) [22], the association between depression and lower numbers of circulating VZV-specific memory T cells may extend to memory T cells specific for antigens of other pathogens that cause disease in older adults, such as influenza viruses and mycobacteria. If so, these observations suggest that untreated depression may identify a subgroup of elderly persons likely to respond poorly to other vaccines (eg, influenza vaccines). Whereas psychological stress is associated with an attenuated immune response to influenza vaccines in older adults [25], few studies have examined the association between depression and infectious disease risk and/or disease-relevant immunologic endpoints, such as vaccine responses.

Depressed subjects who are on selective serotonin reuptake inhibitor (SSRI) therapy but still symptomatic for depression may be refractory to treatment, which occurs in up to 60% of elderly patients [26, 27]. Given that all but 1 of our treated depressed subjects were using SSRIs, our results suggest that central serotoninergic pathways may play a role in regulating CMI responses to VZV, consistent with SSRI enhancement of natural killer cell activity [28] and normalization of inflammatory cytokine levels [29]. Neurotransmitters such as serotonin modulate CMI at the immunological synapse and by direct activity on T cells [30, 31].

Several limitations require consideration. First, whereas only VZV-RCF was reduced in association with untreated depression at baseline, time-varying analyses showed that untreated depression for the study duration reduced both VZV-RCF and ELISPOT. This difference may reflect an effect of depression on a broad spectrum of VZV-specific memory T cells, which is not detected by the interferon-γ ELISPOT assay (which only measures the response of a subset of these T cells) until untreated depression persists. We and others have shown that VZV antibody levels are not highly correlated with levels of

VZV-CMI [12], and there was no correlation between levels of antibodies to VZV and VZV-CMI at baseline or after immunization in the SPS, possibly due to the fact that B cells and T cells respond to different VZV epitopes [5]. Nevertheless, VZV-RCF has emerged as the strongest immunologic predictor of protection against development and severity of HZ [5]. Second, it is possible that alternative VZV-specific immune responses are better correlates of depression than VZV-RCF. Third, additional factors coincident with depression might modulate VZV-CMI and contribute to these findings, including psychological stress, intercurrent viral infection, or alcohol use.

Elderly individuals are already prioritized for zoster vaccination because of their increased risk for HZ and its complications [4]. In this study, depressed elderly adults who are not being treated with an antidepressant (ie, SSRI) had a diminished capacity to develop increased levels of VZV-CMI in response to zoster vaccine compared to nondepressed controls and depressed individuals receiving antidepressants. Thus, among depressed elderly persons, treatment with SSRI might increase the efficacy of zoster vaccine and, possibly, vaccines against other important pathogens, such as influenza viruses. In addition, diagnosis of depression in the elderly may identify individuals who might benefit from more potent vaccines or multidose vaccination schedules.

Notes

Financial support. This work was supported by the National Institute of Mental Health, National Institutes of Health (R01-MH 55253); the VA Cooperative Study Program, Office of Research and Development, Department of Veterans Affairs; a grant from Merck & Co to the VA Cooperative Studies Program; National Institutes of Health grants R01-AG034588, R01-AG026364, R01-CA119159, R01-HL079955, R01 HL095799, and P30-AG028748 (to M. R. I.); UCLA Clinical and Translational Science Institute (UL1TR000124); the Cousins Center for Psychoneuroimmunology; and the James R. and Jesse V. Scott Fund for Shingles Research.

Potential conflicts of interest. M. J. L. receives research funds, consultation fees, and royalties from intellectual property from Merck and Co. All other authors report no potential conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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