Varicella Zoster Virus – Specific Immune Responses to a Herpes Zoster Vaccine in Elderly Recipients with Major depression and the Impact of Antidepressant Medications by Irwin MR et al., Clinical Infectious Disease, 2013 Feb: 1-9.

I. Background

Varicella Zoster Virus (VZV) is a virus which remains latent in sensory neurons following Varicella infection. Incidence and severity of VZV increase in association with a progressive age-related decline in VZV-CMI (cell-mediated immunity).

Herpes Zoster (HZ) [Shingles] exceeds 1% per year in persons 60 yrs. of age or over – more than a million new cases each year; 1/3 of the population is expected to have HZ during their lifetime. (NEJM 2005: 352:2266-7)

II. Hypothesis of the study

The Depression Substudy of the Shingles Prevention Study (SPS) attempted to show an association between major depression and immune responses to a high-titer live attenuated VZV vaccine, which boosts cell-mediated immunity to the virus and decreases the incidence and severity of HZ.

III. Methods Review

The Depression Substudy was a 2-year longitudinal cohort study in 92 community-dwelling adults 60 years of age or over, who had been already enrolled in the SPS, a large, double-blind, placebo-controlled Veterans Affairs Cooperative zoster vaccine efficacy study.

There were 40 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.

Their VZV-CMI was measured prior to vaccination with Herpes Zoster Vaccine or Placebo, and again at 6 weeks, 1 year, and 2 years post-vaccination. This was done by Responder Cell Frequency (RCF) and by interferon-gamma enzyme –linked immunospot assay (Frequency of VZV-specific interferon-gamma-producing PMBCs [blood peripheral mononuclear cells]). RCF is the frequency of circulating VZV-specific CD+4T cells (no. ofVZV-responding cells per 10-fifth PMBCs). (minimizes bias from bio-insignificant assay viability.)

Statistics were performed with IBM SPSS software for Windows, version 19.

IV. Results

The most important figure is Figure 2 on page 4 of the article. It is a bar graph of the Depression Substudy VZV-responder cell frequency, showing results for the 3 groups at baseline and at 6 weeks, 52 weeks and 104 weeks post vaccination.
There were significant differences at all time points between the “Depressed-NO Therapy” and “Depressed-WITH Therapy” participants, but not between the “Depressed-WITH Therapy and the “NON-depressed-NO Therapy participants. Depressive symptoms and sleep disturbance were significantly lower compared to the 2 depressed groups, while there was similarity between the 2 depressed groups. Severity of depressive symptoms or sleep disturbance was not associated with differences in VCV titers at any time point.

V. Author’s Conclusions

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 NON-depressed controls and to depressed subjects receiving antidepressants, means that these groups may thus be poorly protected by vaccination.

The finding that untreated depression is associated with reduced baseline levels of VZV-immunity, as well as a failure to respond to zoster vaccine, may have implications for the risk of other infectious diseases.

Since all but 1 of the treated depressed subjects were using selective serotonin reuptake inhibitors, central serotoninergic pathways may play a role in regulating CMI responses to VZV, consistent with SSRI enhancement of natural killer cell activity and normalization of inflammatory cytokine levels.

Neurotransmitters such as serotonin modulate CMI at the immunological synapse and by direct activity on T cells.

VI. Author’s Limitations

Only one assay (VZV-RCF) was reduced in association with untreated depression at baseline, time-varying analysis showed that untreated depression for the duration reduced immunity in both assays. This may reflect an effect of depression on a broad spectrum of VZV memory-specific T cells, which are not detected by the interferon-gamma ELISPOT (only measures the response of a subset of these T cells).

VZV antibody levels are not highly correlated with levels of CMI, possibly due to the fact that B cells and T cells respond to different VZV epitopes.

It is possible that alternative VZV-specific immune responses are better correlates of depression.

Additional factors coincident with depression might modulate cell mediated immunity (psychological stress, intercurrent viral infection, or alcohol use.

VII. Reviewer’s Comments
The article sheds some meaningful light on why immunity in the elderly is down, and why it takes longer for them to respond to certain disease threats. A lot of work was done, using multiple assays, and careful screens of patient history. I feel the science of immunology here will have to be elucidated because of different types of memory T cells, the difference in roles of T cells and B cells. There are also more things to be learned about the far-reaching biochemical effects of depression on multiple tissues and cells. This will be laborious due to the number of depressed patients with this specific type of infection and background depression.

VIII. Summary for Possible Practice Implications

Among depressed elderly persons, treatment with SSRI might increase the efficacy of zoster vaccine and possibly, vaccines against other pathogens.

Diagnosis of depression in the elderly may identify individuals who might benefit from more potent vaccines or multidose vaccination schedules.

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