Progress in Preventive Control of Shingles

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SUMMARY

Herpes zoster (Shingles) is a localized disease that results from reactivation of an endogenous varicella-zoster virus (VZV) infection that has persisted in latent form within sensory ganglia following an earlier attack of varicella (chickenpox). The incidence and the severity of shingles and its complications increase with advancing age, in temporal association with an age-related decline in cell-mediated immunity to VZV. Information on the cellular site and mechanism of VZV latency, and on the events that follow reactivation appears to explain many of the clinical features of shingles and to provide a rational basis for the presumption that cell-mediated immunity to VZV plays a critical role in limiting its frequency and severity. This information also provides a clear rationale for early antiviral treatment.

Placebo controlled trials have demonstrated that acyclovir administered within 72 hours of the onset of the shingles rash shortens the period of new vesicle formation, speeds rash healing and decreases the severity of pain during the early phase of the disease. Oral acyclovir does not prevent the development of postherpetic neuralgia (PHN), the most frequent debilitating complication of shingles in older persons. Moreover, the limited absorption of oral acyclovir necessitates the frequent administration of high doses (800 mg every 4 hours). Two prodrugs with much better oral bioavailability, famciclovir and valacyclovir, have been recently licensed for treatment of shingles. After ingestion, these prodrugs are rapidly converted to the active compounds, achieving blood levels that are much greater than those obtained with oral acyclovir. This permits less frequent dosing. The safety and efficacy of famciclovir and valacyclovir have been established in randomized double-blind clinical trials. Like acyclovir, they reduce the duration of virus shedding and accelerate the resolution of lesions and of pain. However, while they may shorten the duration of shingles pain, none of these antiviral drugs appears to be capable of preventing PHN.

The frequency of PHN, like that of shingles, also increases markedly with increasing age. PHN is rare in persons below the age of 50, but complicates more than half of the cases of shingles that occur in persons over 70 years of age. Unfortunately, once it is established, PHN is often refractory to treatment. Thus the best hope of reducing the enormous distress and morbidity caused by PHN is to prevent shingles, and the best hope of doing this appears to be the development of an effective vaccine.

The close temporal correlation between the decline in VZV-specific cell-mediated immunity and the increased frequency and severity of shingles and PHN in older individuals suggests that shingles may develop because VZV-specific cell-mediated immunity falls below some critical threshold. The rarity of second episodes of shingles in immunocompetent persons, together with the observation that shingles induces a marked and sustained increase in VZV-specific cell-mediated immunity, suggest that an episode of shingles may "immunize" against a second attack. Levin et al demonstrated that waning VZV-specific cell-mediated immunity in elderly persons can be stimulated by live attenuated varicella vaccine to levels typical of those observed in younger persons, in whom the incidence and severity of shingles are much reduced. Taken together, these observations have led us to initiate a large double-blind placebo-controlled clinical trial to determine whether vaccination with live attenuated Oka/Merck varicella-zoster vaccine will reduce the frequency and severity of shingles and PHN in the elderly.

This trial, VA Cooperative Study #403: **The Shingles Prevention Study**, will enroll a total of 37,200 subjects age 60 or older at 21 study sites across the United States. **The Shingles Prevention Study** is now up and running, with San Diego as the lead study site. Anyone age 60 or older who has not yet had shingles and who may be interested in participating should call one of our Study Coordinators, Roma Bourne, R.N., or Patty McCook, R.N. at (619) 642-6286.