



Novel vaccine promising in treatment of genital warts

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Baltimore — Phase II study results point to the potential role of HspE7 as a safe and effective immunotherapeutic agent for the treatment of genital warts and other HPV-related sexually transmitted diseases, Keerti V. Shah, M.D., said.

HspE7 is a fusion product linking *Mycobacterium bovis* BCG heat shock protein (Hsp) with HPV 16 E7 that was designed to invoke the cellular immune response necessary to eradicate HPV-infected cells. HSPs are immunogenic compounds important as regulators of immune response to cancers and infectious agents, and in the vaccine construct serve as an adjunct to deviate the immune system in the direction of cellular immunity. E7 is an antigenic protein found in all HPV types and is expressed in HPV-infected transformed dysplastic epithelial cells where it is important for maintaining abnormal cell division.

Efficacy of HspE7 in the treatment of genital warts was first noted in a post-hoc analysis of data from a study investigating its use for patients with anal dysplasia caused by HPV 16. In that investigation, enrolled subjects with coexisting internal and external genital warts were noted to experience reduction in wart area over time and eventually resolution of those lesions. The efficacy of HspE7 for treating genital warts was then corroborated in a prospective, randomized, double-blind, placebo-controlled study.

"Although this vaccine was originally designed for treatment of diseases caused by HPV 16, it appears to have broad activity in disorders associated with other HPV types, particularly HPV 6 and 11 that cause genital warts. The response of the genital warts to HspE7 takes time, but importantly, there have been very few recurrences and the treatment is very well tolerated, causing only mild-to-moderate injection site reactions. Additional study and longer follow-up is needed to more fully characterize the activity of HspE7 in the treatment of genital warts, but this agent is definitely worthy of further evaluation," said Dr. Shah, professor, molecular microbiology and immunology, Johns Hopkins University

Bloomberg School of Public Health, Baltimore, and co-director, Johns Hopkins Center for the Study of Sexually Transmitted Diseases.

HspE7 has been administered as three subcutaneous injections at one-month intervals. In the initial study enrolling patients with anal dysplasia, 26 patients had concomitant genital warts and 23 could be evaluated for a potential response to study medication. Among patients treated with the highest evaluated dose, 500 mcg, 90 percent demonstrated reduction in wart area at six months after their first HspE7 injection. During serial follow-up visits at

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three-month intervals, the wart area progressively diminished and among patients evaluated at 18 months, 73 percent had experienced complete clearance of their genital warts. For those patients experiencing complete remission of their warts, none developed a recurrence during 15 months of follow-up.

The prospective, randomized, double-blind, clinical trial of genital wart treatment was undertaken in 54 patients and assessed efficacy using the primary endpoint of reduction in wart area at six months. Based on the retrospective analysis, it was projected that HspE7-treated patients would achieve a 50 percent reduction in wart size at the end of the follow-up; placebo-treated patients were expected to have no more than a 25 percent decrease.

The six-month outcomes, however, exceeded those estimates and showed a 53 percent

reduction in wart size in the HspE7 group compared with only a 16 percent decrease among the controls. In addition, the active treatment was associated with a 36 percent complete response rate, which was also better than that observed among the patients in the anal dysplasia trial.

"We are very pleased with the results of this study, and are in the midst of strategic planning for the future development of HspE7. In particular, we would like to investigate this product for the treatment of laryngeal papillomatosis, but studies of genital wart treatment are also high on our list," said John R. Neefe, M.D., vice president, clinical research and regulatory affairs, Stressgen Biotechnologies, Victoria, B.C.

The finding that HspE7 was effective in treating genital warts, which are associated with HPV 6 and 11, came as a pleasant surprise to the researchers. While they did not expect that activity from the outset, neither had they ruled it out.

"We had assumed there would not be cross-reactivity for these different HPV types, although nobody really knew what the potential would be with a cellular immune response. In retrospect, however, we see there is enough similarity between E7 of HPV 6, 11, and 16 that cross-reactivity might be predicted," Dr. Neefe commented.

Having found that creating immunity to E7 from HPV 16 is also effective against E7 from other genital HPV types, Dr. Neefe said he wouldn't be surprised if HspE7 might also have efficacy in the treatment of cutaneous warts. That hypothesis has not been tested, however, and for now, Stressgen is not planning to pursue an indication for cutaneous warts.

Preliminary studies have been conducted demonstrating that HspE7 treatment induces cellular immunity in humans, and further research in that area is planned. However, there is a wealth of preclinical evidence showing administration of HspE7 induces antigen-specific cellular immunity that is necessary for a treatment effect, noted Dr. Neefe.

Dr. Shah is an adviser to Stressgen. **DT**