Search for HPV Treatment Vaccine Heats Up, Researchers Optimistic

Will there ever be a vaccine to treat cervical cancer? If the number of candidate vaccines is any indication, the answer is yes.

Researchers set their sights on a therapeutic vaccine for cervical cancer more than a decade ago when they learned that the disease is caused by a virus. But treatment vaccines targeted at the cancer culprit, human papillomavirus (HPV), have progressed slowly compared with HPV prevention vaccines, whose development began at the same time. Although two preventive vaccines are now speeding toward regulatory approval, no treatment vaccine has yet made it beyond a phase II trial.

Recently, though, three companies have announced plans to follow up on phase II studies with randomized trials which, though not yet phase III, could be important for this field. In April, Transgene Inc., MGI Pharma, and Stressgen Biopharmaceuticals Corp. all issued optimistic statements based on recent successes in early phase II trials focused on high-grade cervical dysplasia.

“We are extremely pleased by [our] results,” said Transgene’s chief executive officer, Philippe Archinard, in a press conference. MGI Pharma and Stressgen have expressed similar confidence in briefings and Web postings in the last few months.

The slow progress to this point has not been for lack of trying. Lab researchers have examined many diverse strategies to induce the T-cell response that could be essential to a successful immune system assault on cervical cancer cells. Concentrating on T cells—the other key weapon of the immune system, antibodies, will not work against cervical cancer cells—they have tried viral and bacterial vectors, fusion proteins, peptides, and DNA-based and dendritic cell–based vaccines, and more. Many have looked promising in the laboratory.

“Vaccine results in HPV-induced mouse tumors are absolutely excellent,” said W. Martin Kast, Ph.D., an immunotherapy researcher at Norris Comprehensive Cancer Center in Los Angeles. “It is beautiful in so many labs; you’re able to get rid of existing tumors.”

But time after time, results in the clinic have not lived up to expectations. Kast, who reviewed therapeutic HPV vaccine research at the annual meeting of the American Association of Cancer Research in April, counts 21 phase I or I/II trials that have been published, most with disappointing results. In late-stage cervical cancer, where new drugs are usually tested, there are still no positive results, he said.

The one bright spot is that some therapeutic vaccines have shown signs of effectiveness against precancerous lesions, known as cervical intraepithelial neoplasia (CIN) 2 and CIN3. The three companies now planning large randomized trials have had their successes in this population.

The disadvantage of focusing on this stage is that there is already a routine, fairly simple, outpatient treatment for CIN2 and 3 called loop electrosurgical excision procedure, or LEEP. Vaccine proponents point out, however, that about 10% of lesions recur after LEEP and that the procedure carries some risk of cervical damage. Besides, they say, patients would benefit from a choice of treatments.

LEEP, as Archinard pointed out, “never comes with pleasure to the patients.”

Transgene, based in Strasbourg, France, is testing a therapeutic vaccine called TG4001. It uses the modified vaccinia virus Ankara (MVA) to deliver two proteins, E6 and E7, which are the targets in virtually all the therapeutic vaccines developed to date. Unlike many other HPV proteins, E6 and E7 continue to be expressed in HPV-infected cells that have transformed into cancer cells. Transgene’s candidate vaccine is targeted at E6 and E7 specific to HPV16, the type of the virus most often found in cervical
cancers. In the company’s recently completed phase II trial, nine of 18 women had complete responses after three subcutaneous injections with TG4001, which includes interleukin 12 as adjuvant, added to boost the immune response.

Among the nine women with complete responses, their CIN2 and CIN3 lesions disappeared, and no E6 or E7 microRNA was detected. Although the sample was not large enough for these results to reach statistical significance, Archinard is optimistic.

Transgene is now talking to regulatory agencies in the United States and Europe about the design of its next trial. Archinard said in an interview that it was too early to say whether it would be a larger phase II or a phase III trial but that it likely will include different age groups and patients with other HPV types. The company hopes to have the trial design settled by the end of July and a corporate partner by the end of the year.

Another company looking beyond phase II is MGI Pharma, based in Bloomington, Minn., which last year acquired ZYCOS Inc. and its therapeutic vaccine candidate ZYC101A. Now called Amolimogene, the vaccine contains plasmid DNA-encoding fragments from the same E6 and E7 proteins. This candidate targets both HPV16 and HPV18, the second most common type in cervical cancer.

Phase II results for the vaccine, published in Obstetrics and Gynecology in February 2004, were mixed. The lead author, Francesco Garcia, M.D., of the University of Arizona in Tucson, and colleagues at other clinical centers tested the vaccine in 161 women who were randomized to receive 100 mg or 200 mg of the drug or a placebo. About 43% of women in the vaccine groups had their lesions resolved compared with 27% in the placebo group—not a statistically significant difference.

But in a subgroup of 43 women younger than 25 years, about 70% of lesions resolved versus 23% with the placebo. On the basis of these data, MGI Pharma announced that it is going forward with a “pivotal program.” The first part, now under way, is a multicenter, randomized, phase II trial that will enroll 300 patients aged 25 years or younger with CIN2 or 3. The patients will receive one 200-mg injection of Amolimogene, three 200-mg doses, or a placebo. A second randomized trial, to follow, will probably use the chosen dose in a broader population, including older women, said Daron Ferris, M.D., of the Medical College of Georgia in Augusta, who is participating in the trial.

The third vaccine headed for an advanced trial is a fusion protein, HspE7, developed by San Diego–based Stressgen. HspE7 combines the viral protein E7 with a heat shock protein to seek out dendritic cells. The dendritic cells then present E7 to T cells, inducing them to recognize and attack the E7-containing cancer cells.

In a summary of phase II trial results, presented last year at the Society of Gynecologic Oncologists annual meeting, Mark Einstein, M.D., of Albert Einstein College of Medicine in New York, reported that 22 (71%) of 31 patients responded after receiving three 500-mg injections of HspE7 over 60 days.

Stressgen had originally planned a phase III trial in early 2006 on the basis of these findings. But that plan was revised when the company found that a reformulated version of HspE7 combined with low concentrations of an adjuvant showed much more promise than the original version.

“We have impressive preclinical data with the new formulation,” said CEO Gregory McKee in a conference call with investors in April. “It is 10 times more potent than the original.” McKee declined to name the adjuvant, saying that the company was still preparing its patent application for the combination.

A phase I/II randomized trial in 400 patients is slated to begin early next year, McKee said. The trial will compare the reformulated vaccine to a placebo and to adjuvant alone, probably in women with high-grade CIN. Stressgen may choose to first test the concept in patients with genital warts, which is caused by two other types of HPV, he said.

**More in the Pipeline**

Even as the three front-runner vaccines move forward, preclinical and early clinical work on other candidates continues elsewhere. In Australia, for instance, Ian Frazer and colleagues at the University of Queensland are working with a virus-like particle vaccine, as is used in the prophylactic vaccine developed there, sponsored by Merck, and recently approved by FDA. Combined with conventional therapy, this vaccine is now in a phase II randomized trial as a therapy for genital warts. If that trial proves successful, Frazer said in an e-mail, “the intent would be to proceed to a similar trial in cervical lesions.”

Another strategy is being pursued at the University of Arkansas for Medical Sciences in Little Rock, where Alessandro D. Santin, M.D., and colleagues are working on a therapeutic vaccine based on autologous dendritic cells loaded with the full-length E7 protein for HPV16 and -18. That vaccine, supported by an NCI grant, is now in a phase I trial for women with early-stage invasive cervical cancer—one of the few candidates not focusing on the precancerous lesions. The study has finished collecting data and final results are expected in the next few months, Santin said.

And in Los Angeles, Norris researchers are pursuing a new approach focused on Langerhans cells, another immune system network that can induce T-cell responses. Kast and colleagues have identified a specific pathway in Langerhans cells that HPV uses to evade the human immune system.

“If my hypothesis is right, the virus is trying to escape the immune response by switching on the phosphoinositide 3-kinase [PI3] pathway in the Langerhans cells,” Kast said, and that means the PI3 kinase pathway could be a target for therapy. In support of this hypothesis, a PI3 kinase inhibitor blocked activation of the pathway in vitro, enabling the Langerhans cells to initiate a response to HPV.

More preclinical work needs to be done before a PI3-kinase inhibitor can join the ranks of promising treatments in trials for HPV-induced cancers. But those ranks still seem to be wide open to new candidates.

“There is still no clear, winning strategy,” Kast said. But there will be, he added. “Just give it time.”

—Caroline McNeil