Human Vaccines & Immunotherapeutics 10:7, 1773–1777; July 2014; © 2014 Landes Bioscience

Human Vaccines & Immunotherapeutics: News

Direct injection vaccine treatment of pancreatic cancer results in stable disease

Researchers from Rutgers Cancer Institute of New Jersey recently presented promising data from a Phase 1 clinical trial of an immunotherapeutic vaccine for pancreatic cancer, injected directly into the tumor. The results suggested an encouraging period of stable disease in vaccinees. Preliminary results of the Phase 1 trial were presented at the AACR Pancreatic Cancer: Innovations in Research and Treatment conference held in New Orleans.

The investigational vaccine PANVAC contains additional genes selected to stimulate a person's immune system to recognize and develop an immune response to the disease. Two types of PANVAC were utilized in the Phase 1 trial: (1) PANVAC-V, which uses the same virus as the smallpox vaccine, is a live attenuated vaccinia vaccine that is given in the arm, and (2) PANVAC-F, a live Fowlpox virus that cannot replicate, is injected directly into the tumor and subsequently into the arm as a booster. Direct tumor injection took place through an endoscopic ultrasound, in which a scope was inserted through the mouth and into the stomach so that the tumor in the pancreas could be seen.

The Phase 1 trial, conducted at the Cancer Institute of New Jersey, included 14 patients who were not candidates for surgery to remove their cancer. During the first phase of the study, patients were evaluated for toxicity, tumor progression and the presence of tumor markers for pancreatic cancer. Due to rapid disease progression, two patients were removed from the first part of the study after two weeks. The second part of the trial involved giving a higher dosage of PANVAC-F during direct injection of the tumor. During this phase, one patient was removed due to rapid disease progression and died one month later, while a second patient withdrew and died after 16 mo. Of the remaining 10 patients from both dose levels, three were shown to have metastatic disease with a survival range of 6–22 mo. The other seven patients presented without distant metastasis with a survival range of 4–36 mo. Of this latter group, none developed metastatic disease but instead died of a secondary condition associated with locally progressive pancreas cancer. All but one of the ten patients transitioned to treatment with a standard therapy for pancreas cancer (gemcitabine).

"While the median survival rate for patients without distant metastasis was nearly a year-and-a-half with this treatment, there was one patient whose disease remained clinically stable for nearly three years. When you have a disease that carries a five-year 6% survival rate, these findings are very encouraging and will hopefully lead to more effective ways of managing and treating this disease," the researchers commented.

Oral cholera vaccine confers 86% protection during outbreak in Guinea

A new study, published in the N*ew England Journal of Medicine*[1] showed that the oral cholera vaccine Shanchol provided 86% protective efficacy during a recent outbreak in Guinea.

The study was conducted by Epicenter (the research arm of the international medical humanitarian organization Doctors Without Borders) and the Guinean Ministry of Health. As the first study on cholera vaccines ever conducted during an outbreak in Africa, the study evaluated the efficacy of two complete doses of Shanchol in the first months after administration. During a cholera outbreak in Guinea in 2012, investigators administered 316,250 doses of Shanchol in two rounds in the coastal districts of Boffa and Forecariah over a 6-wk period beginning in April. The vaccination campaign achieved high coverage rates with 76% in both Boffa and Forecariah. High coverage was shown to reduce disease transmission in the vaccinated communities. Most of the confirmed cholera cases were from a small outbreak in a local community that had the lowest vaccination coverage. Suspected cholera cases were confirmed by rapid test, and then teams confirmed how many of these people had been vaccinated. Vaccination with two complete doses of Shanchol was associated with significant protection (86%) against cholera.

"Because we had never documented the effectiveness of this new vaccine in real-life epidemic conditions, we did not have enough information to understand the potential of this vaccine as a tool to control a cholera outbreak," said Dr Francisco Luquero, principal investigator of the study. "Now we know that oral cholera vaccine confers a high level of protection in outbreak settings, and that vaccinating against this highly deadly disease can and should be one thing we do when we have a cholera epidemic on our hands, in addition to other preventive and control measures."

The World Health Organization (WHO) has pre-qualified two oral cholera vaccines, Shanchol (produced by Shantha Biotechnics) and Dukoral (Crucell). Of the two, Shanchol is considered more appropriate for use in developing countries, because it is much more affordable, easier to produce, and easier to transport and keep in storage. In 2010, oral cholera vaccine was added to the WHO recommendation for cholera prevention and control, and in 2013, the WHO set up an emergency stockpile of Shanchol. However, the vaccine has not been commonly used as a public health tool for control of the disease. The new study has the potential to change this.

"The results, on both the effectiveness and feasibility of oral cholera vaccines during an actual emergency, will hopefully bolster efforts to integrate vaccines in the global response to cholera outbreaks," said Dr. Rebecca Grais, senior author of the NEJM paper. „Until very recently, cholera vaccines have not been considered among the tools to use in outbreak control. Several deadly and large-scale cholera epidemics have shown the

limits of the traditional outbreak response to contain national-scale epidemics. The use of oral cholera vaccine should greatly improve our ability to prevent and control epidemics, and ultimately, to save more lives."

Reference

1. Luquero FJ, et al. Use of Vibrio cholerae vaccine in an outbreak in Guinea. N Engl J Med. 2014; 370:2111-20

Massive blast of measles vaccine successfully fights cancer

An experimental trial using a very high dose of measles vaccine to treat blood cancer provides the proof-of-concept that a single massive dose of intravenous viral therapy can kill cancer by overwhelming its natural defenses. The preliminary but exciting results were published recently in the journal *Mayo Clinic Proceedings*.[2]

Researchers have known for decades that viruses can be used to destroy cancer. They bind to tumors, use them as hosts to replicate their own genetic material, and evetually the cancer cells die and release the virus. Viral vaccines can produce the same effects. In addition, they can be modified to carry radioactive molecules to help destroy cancer cells without causing widespread damage to healthy cells around the tumors. Any remaining cancer that carries remnants of the vaccine's genetic imprint, will be attacked by the body's immune system.

In the past, a variety of cancer-killing viruses, including herpes and poxvirus, have been tested in rodents where they have produced long-lasting cures. But when tested in humans, the systemic activity observed in rodents was reduced. Researchers have also observed that there seems to be a threshold level of virus that is reqired to defeat the defense mechanism in cancerous tumors. The new study, led by Dr Stephen Russell from the Mayo Clinic, could help define this level.

Two measles-seronegative patients with relapsing drug-refractory myeloma and multiple glucose-avid plasmacytomas, were treated by intravenous infusion of 1011 TCID50 (50% tissue culture infectious dose) of measles vaccine. This is enough measles vaccine to inoculate 10 million people. The strain used (MV-NIS) was isolated in 1954 from the throat of an 11-y-old boy and has been used to safely make widely used measles vaccines. Both patients responded to therapy with M protein reduction (an abnormal protein in the urine or blood, often seen seen in multiple myeloma) and resolution of bone marrow plasmacytosis. Noteably, one patient experienced durable complete remission at all disease sites. Tumor targeting was clearly documented by NIS-mediated radioiodine uptake in virus-infected plasmacytomas. Toxicities resolved within the first week after therapy. The study authors conclude that oncolytic viruses offer a promising new modality for the targeted infection and destruction of disseminated cancer.

"It is a landmark," Dr Russell told the StarTribune. "We have known for a long time that we can give a virus intravenously and destroy metastatic cancer in mice. Nobody has shown that you can do that in people before."

The vaccine had previously been tested in lower doses in other cancer patients, but only worked when the massive dose of 1011 infectious units was used. It is important that the high dose is given to start with, because for now there is no second chance. Once the vaccine has been delivered, the immune system will recognize and attack it. Actually, most people have been inoculated with measles vaccine, rendering it susceptible to the immune system. But patients with multiple myeloma often have suppressed immune systems, which can allow the virus to work.

Dr Russell said that breaking down the immune system before the treatment will be part of another upcoming clinical study. The Mayo Clinic expects to launch a bigger trial later this year to see if the massive measles vaccine dose works in a larger number of patients.

Reference

2. Russell SJ, et al. Remission of disseminated cancer after systemic oncolytic virotherapy. Mayo Clin Proc 2014; 89:926-33

Favorable phase 2 results for Sanofi's *Clostridium difficile* vaccine

Sanofi Pasteur recently presented positive Phase 2 trial results for its investigational vaccine for the prevention of *Clostridium difficile* infection (CDI). Primary objectives were met and observed adverse events were mild. The vaccine generated an immune response against *C. difficile* toxins A and B, which are largely responsible for the symptoms of CDI. Results were presented at the recent American Society for Microbiology Meeting in Boston.

The spore-forming potentially life-threatening bacterium *C. difficile* is a common cause of intestinal disease. Symptoms range from fever to diarrhea and often include dehydration, nausea and abdominal pain. Complications may include perforation of the colon, sepsis, life-threatening pseudomembranous colitis and toxic megacolon, a lethal condition. The risk of contracting CDI increases with age, antibiotic treatment, and time spent in hospitals or nursing homes.

The randomized multi-center Phase 2 vaccine study was divided into two stages. The first stage with 455 volunteers was placebo-controlled and double-blind and designed for dose and formulation selection. The second stage with 206 volunteers was designed to compare the dose and formulation chosen in the first stage against two alternate dosing schedules. Study participants were adults aged 40–75 y who were at risk of CDI due to impending hospitalization or residence in a long-term healthcare facility.

In stage 1, volunteers were randomized into one of five study groups: high-dose or low-dose vaccine either with or without adjuvant, or placebo. Each formulation was administered on days 0, 7 and 30. The group that received high-dose vaccine plus adjuvant generated the stringest immune response and was selected for further study of different administration schedules (days 0, 7 and 30; days 0, 7 and 180; days 0, 30 and 180). Increased immune responses were observed in all vaccine groups and with each dose, but overall, administering the vaccine on days 0, 7 and 30 produced the most favorable immune profile, particularly in volunteers aged 65–75 y. All tested vaccine doses and schedules had an acceptable safety profile throughout the Phase 2 study.

"In this trial, we saw a significant increase in antibody production against *C. diff* toxins, across all dosing schedules and volunteer ages," said Dr Guy De Bruyn, Director, Clinical Development, Sanofi Pasteur. "These results provide a strong foundation for our efforts to develop and offer a vaccine to prevent first occurrence CDI."

Based on the Phase 2 results, the high-dose plus adjuvant vaccine formulation administered on days 0, 7 and 30 was selected for further evaluation in Phase 3. For this late stage trial, which was initiated in August last year, Sanofi is recruiting 15,000 participants in 17 countries. Pfizer and Valneva are also developing vaccines against C. diff, but both are still in early clinical trials.

Amgen's oncolytic immunotherapy promising as single agent or combination therapy

Amgen recently announced new data from two key clinical trials of talimogene laherparepvec (also known as T-Vec), an investigational oncolytic immunotherapy. T-Vec was tested as both a single agent and as part of a combination regimen in patients with metastatic melanoma. The findings were presented at the 50th Annual Meeting of the American Society of Clinical Oncology (ASCO) in Chicago.

In a multicenter, open-label Phase 1b/2 trial, T-Vec was tested in combination with ipilimumab in 19 patients with unresected stage IIIB-IV melanoma, no prior systemic treatment, measurable disease, and more than one injectable cutaneous, subcutaneous or nodal lesion. T-Vec was administered by intratumoral injection on weeks 0 and 4 and every two weeks thereafter. Ipilimumab was administered intravenously on weeks 6, 9, 12 and 15. Patients were treated with T-Vec until complete response, all injectable tumors disappeared, disease progression per a modified immune-related response criteria (irRC), or intolerance of study treatment. Tumors either shrank in size or were no longer detectable in 56% of patients when T-Vec was given prior to and in combination with ipilimumab. The data showed no dose-limiting toxicities with T-Vec in combination with ipilimumab. The most common adverse events observed were chills, fevers, rash and fatigue.

T-Vec was also tested in a global, randomized, open-label Phase 3 trial to evaluate its safety and efficacy as a single agent against melanoma. The trial included over 400 patients with unresected stage IIIB, IIIC or IV melanoma. They were randomized 2:1 to receive either T-Vec intralesionally every two weeks or a control therapy (granulocyte-macrophage colony-stimulating factor; GM-CSF) subcutaneously for the first 14 d of each 28 d cycle. Treatment could last for up to 18 mo. Where appropriate, stable or responding patients could receive additional treatment on an extension protocol. The primary endpoint was durable response rate defined as the rate of complete response or partial response lasting continuously for six or more months, as compared with control therapy. Overall survival (OS) was a secondary endpoint. The pivotal Phase 3 trial met its primary endpoint showing a statistically significant improvement in durable response rate (16% in the vaccinated group vs. 2% in the control group). Among the 26% of patients who achieved an overall response in the T-Vec group, 40% achieved a complete response (no evidence of disease). Among the T-Vec responders, there was a 65% probability of responses lasting for at least 12 mo. Looking at the key secondary endpoint, OS, the results demonstrated a 4.4 mo improvement in OS, which closely approached statistical significance in the total patient population tested that included patients with and without visceral tumors. Most frequently observed adverse events in this trial were fatigue, chills and pyrexia. The most common serious adverse events included disease progression, cellulitis and pyrexia.

"We are entering an era where new melanoma therapies are advancing clinical care for patients in ways not previously seen," said Dr Sean E. Harper, executive vice president of R&D at Amgen. "Talimogene laherparepvec has demonstrated the ability to produce durable and complete responses in patients with metastatic melanoma which provides a strong basis for a filing later this year and potential approval of talimogene laherparepvec as a novel treatment for this devastating disease."

The investigational oncolytic immunotherapy talimogene laherparepvec is designed to selectively replicate in tumors (but not normal tissue) and to initiate an immune response to target cancer cells that have metastasized. T-Vec works in two important and complementary ways. First, it is injected directly into tumors where it replicates inside the tumor cells causing lysis. The lysis of the cancer cells can release tumor-derived antigens, along with GM-CSF, that can stimulate a systemic immune response where T cells are able to target metastatic cancer.

GAVI needs $7.5 billion to fully fund immunization programs until 2020

At a recent meeting in Brussels, the GAVI Alliance called on donors to back ambitious plans to immunize an additional 300 million children against potentially fatal diseases during 2016–20, thereby saving a further 5–6 million lives. To achieve this, GAVI will require $7.5 billion in addition to the $2 billion in hand for that period. GAVI highlighted the economic benefits of fully funded, sustainable vaccine programmes.

Despite an unprecedented increase in vaccine programs in developing countries, 1.5 million children die each year of vaccine-preventable diseases, and one in five children worldwide do not receive a full course of even the most basic vaccines. Together with their partners, GAVI has managed to put developing countries on track to immunize close to half a billion additional children during 2000–15, saving approximately six million lives. Additional investments for the 2016–20 period could double the total number of lives saved with GAVI-supported vaccines since 2000.

Besides the ethical aspects of protecting children against illness, the GAVI Alliance points out that the economic benefits of fully-funded sustainable vaccine programs would

result in $80–100 billion in gains for developing countries through increased productivity and reductions in the cost of treating vaccine-preventable illnesses. As GAVI-supported countries grow more prosperous, they can assume greater responsibility for their immunization programs. Between 2011 and 2015, countries have contributed ~$470 million. This number will grow to $ 1.2 billion during 2016–20, making developing countries one of the largest contributors to the Alliance. By 2020, it is projected that 22 countries will have graduated and taken over full financing of their GAVI-supported vaccines, marking a new era of increased sustainability.

"We are faced with an historic opportunity to support countries to build sustainable immunisation programs that will protect entire generations of children," said Dagfinn Høybråten, Chair of the GAVI Alliance. "The investments we all make now can ensure the equivalent of two children every second will be reached with GAVI-supported vaccines for five years and secure the future health and economic prosperity of all our children in years to come."

Importantly, the GAVI Alliance does not simply rely on contributions from sovereign and corporate donors. Through its effective public-private partnership model, GAVI also successfully works out developing countries' co-financing commitments, and negotiates with vaccine manufacturers to reduce prices for GAVI-supported countries.

In 2013, GAVI secured a record low price of $ 4.50 per dose of HPV vaccine, meaning that a full three doses course would cost only $13.50. Since more evidence suggests that two doses also offer sufficient protection, a full course would cost only $9, which is far less than $100+ that the shot can cost privately.

The Children's Investment Fund Foundation (CIFF) recently agreed to invest $25 million in GAVI's HPV vaccination programs to protect girls and women in developing countries from HPV infection as the leading cause of cervical cancer. The funding will be matched by the UK Department for International Development through the GAVI Matching Fund.

"Our investment in the GAVI Alliance will have a major impact on the lives of women and families in developing countries," said Dr Michael Anderson, CEO of CIFF. "HPV vaccine brings a double benefit for adolescent girls. Not only does it protect them from a terrible disease but it gives them the opportunity to access health services and engage with healthcare professionals, in many cases for the first time in a number of years."

More than a quarter of a million women die of cervical cancer every year, and 85% of them live in low-income countries, according to the latest statistics published by the International Agency for Research on Cancer (IARC). Without changes in prevention and control, cervical cancer deaths are expected to rise to 416,000 by 2035, with > 95% expected to be women living in poor countries. The GAVI Alliance is supporting 23 countries that are undertaking or have received approval for HPV programs.

"Cervical cancer is a devastating disease that kills women at exactly the time when their families need them most," said GAVI's CEO, Dr Seth Berkley. "I am pleased that CIFF is showing incredible support for our goal of reaching 30 million girls in 40 countries with this vital vaccine by 2020."

Computer model helps vaccinate more kids at lower cost

A new computational modeling and simulation software called HERMES (Highly Extensible Resource for Modeling Supply chains) has been used to help the Republic of Benin in West Africa determine how to bring more lifesaving vaccines to its children. The findings were published in a recent issue of the journal *Vaccine*.[3]

HERMES was developed by researchers from University of Pittsburgh and Johns Hopkins Bloomberg School of Public Health. This software platform allows users to generate a detailed discrete event simulation model of any vaccine supply chain. It can serve as a ‚virtual laboratory' for policy makers, health officials, funders, investors, vaccine and other technology developers, manufacturers, distributors, logisticians and researchers to address a variety of questions in supplying vaccines as well as other health supplies.

In the case of Benin, the HERMES model has been used to show the impact of adding rotavirus vaccine to the nation's supply chain. Rotavirus is a major cause of infant mortality in developing countries, killing nearly half a million children annually, with the highest death rates in Africa and South Asia. HERMES was also used to evaluate different options of redesigning the Benin vaccine system being considered by the Benin Ministry of Health. The impact on cost and vaccine availability of four possible options was explored: (1) maintaining the current system, (2) consolidating the nation's system of 80 commune-level supply depots to a system of 34 health-zone depots, (3) removing the commune level completely, and (4) removing the Commune level and expanding to 12 department stores.

The computational model favored the health zone approach along with changing transportation routes, which was estimated to save $50–70,000 in initial expenses and $50–90,000 in annual costs compared with the other scenarios, while still reaching > 99% of children. Through 2017, the improved plan would save Benin > $500,000 in total costs while improving vaccination rates and facilitating the rotavirus vaccine.

"The paper outlines our engagement with the Benin Ministry of Health in which we worked to choose among some key redesign options of their vaccine supply chain," said Dr Shawn Brown, Technical Lead of the HERMES team and first author. "It is a clear use of computational modeling and simulation to help a government figure out how to get the vaccines that are so desperately needed to every child they can."

Results from the HERMES model have helped Benin enact some initial changes in their vaccine delivery system, which may lead to further changes nationwide.

Reference

3. Brown ST, et al. The benefits of redesigning Benin's vaccine supply chain. Vaccine 2014; 32:4097-103

Conclusive proof: immunizations do not cause autism

A new meta-analysis of 1.25 million children vaccinated worldwide against a variety of diseases found that vaccines are not associated with autism. Results were published in a recent issue of the journal *Vaccine*.[4]

Since the British gastroenterologist Andrew Wakefield first postulated a link between childhood vaccinations and the subsequent development of autism in 1998, there has been enormous debate about this issue. While his findings were later determined to be fraudulent, many parents still believe in them and refuse to vaccinate their children. This has become a major public health issue with vaccine-preventable diseases increasing in the community due to the fear of a link between vaccinations and autism.

An Australien team of researchers performed a meta-analysis to summarize available evidence from case-control and cohort studies on this topic. Eligible studies assessed the relationship between vaccine administration and the subsequent development of autism or autism spectrum disorders (ASD). Five cohort studies involving 1,256,407 children and five case-control studies involving 9,920 children were included in this analysis. The cohort data revealed no relationship between vaccination and autism or ASD, nor was there a relationship between autism and MMR (measles-mumps-rubella vaccine), or thimerosal, or mercury (Hg). Similarly the case-control data found no evidence for increased risk of developing autism or ASD following MMR, Hg, or thimerosal exposure.

From these findings, the authors conclude that vaccinations are not associated with the development of autism or autism spectrum disorder. Furthermore, the components of the vaccines (thimerosal or mercury) or multiple vaccines (MMR) are not associated with the development of autism or autism spectrum disorder.

The senior author of the study, Dr Guy Eslick from the University fo Sydney, told *The New York Post*: "The data consistently show the lack of evidence for an association between autism, autism spectrum disorders and childhood vaccinations … providing no reason to avoid immunization on these grounds."

Dr Eslick stressed that he had no vested interest in the argument, in that he is not an expert in vaccination or autism and his study was not funded by a drug company. "I did this because it was really interesting to me that there is a mass of people against vaccination and there really wasn't any information to support that," he said. "I want my research to elucidate the truth and find out what is real".

Reference

4. Taylor LE, et al. Vaccines are not associated with autism: an evidence-based meta-analysis of case-control and cohort studies. Vaccine 2014; 32:3623-9