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World Vaccine Trials Congress 2012

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"The World Vaccine Trials Congress 2012 provided a rare opportunity to hear from a diverse group of professionals all working in the area of vaccine trial design and implementation."

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The successful design and implementation of vaccine clinical trials is a long and complicated process. Determining trial size, choosing an appropriate end point, managing diverse trial sites, and collecting detailed safety data are just some of the challenges faced along the way. At the World Vaccine Trials Congress 2012, presenters from academia, government agencies, industry and nonprofit organizations described their experiences dealing with these challenges. Also highlighted were newer issues related to the increasing globalization of infectious disease vaccine trials, the clinical development of promising cancer vaccines, and the emergence of electronic data-collection tools. The conference thus provided valuable insights into the present and future of the vaccine trial enterprise.

David McIntosh (Novartis) opened the conference with an excellent overview of the current problems and recent advances in vaccine development. He discussed traditional problems, such as the difficulties of using immunogenicity data to accurately predict vaccine efficacy, and also covered future challenges, such as the need to develop vaccines suitable for pregnant women, immunocompromised patients and healthcare workers. McIntosh also reviewed the development of a meningococcal serogroup B vaccine at Novartis, which was designed by systematically determining the key bacterial surface antigens for vaccine incorporation. He expressed optimism that such a 'reverse vaccinology' approach might also be used to produce vaccines against other pathogens in the future. In addition, McIntosh highlighted the development of electronic devices as an important tool for improving patient recruitment while reducing trial costs.

Vaccine efficacy studies in animal models

Determining vaccine efficacy early in development is critical, and reliable animal models are often central to this task. With this in mind, three researchers presented preclinical data from vaccine studies in primate and transgenic mouse models. Sujan Shresta (La Jolla Institute for Allergy and Immunology) described her successful use of cytokine receptor knockout mice to study the antibody-dependent enhancement of dengue virus pathogenesis. Monica Vaccari (National Cancer Institute) presented rhesus macaque studies in which she varied the challenge dose and route of simian immunodeficiency virus infection in order to improve our understanding of HIV transmission. Jonathan Fallon (National Cancer Institute) showed data from his colleagues' cancer vaccine studies in mice. These studies utilized the ApcMin/+ transgenic mouse model of spontaneous colorectal cancer, and demonstrated strong efficacy for a poxviral-based cancer vaccine in combination with a COX-2 inhibitor. All of these presentations emphasized that animal models can be used to study specific aspects of human immunity or disease, even if the model does not comprehensively mimic the human disease.

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Clinical trial design & appropriate patient selection

Several clinicians who design vaccine clinical trials also shared their experiences and insights. A consistent theme of these presentations was the need to move beyond testing merely for vaccine efficacy, and to maximize the amount of useful information learned from every trial. Such information can improve the design of subsequent clinical trials as a vaccine's development advances, and also allow bench scientists to retool their efforts if a vaccine is found to be ineffective.

James Kublin (Fred Hutchinson Cancer Research Center) gave an excellent presentation on his work in designing HIV vaccine trials. Because it is unclear which of the many HIV vaccines in development will be most effective, he has devised innovative trial designs to test multiple candidate vaccines simultaneously. One advantage of these adaptive trial designs is that they allow vaccine developers to quickly identify a highly ineffective vaccine and replace it with another candidate.

Mark Ahn (Galena Biopharma) described his company's progress towards developing a HER2/neu peptide-based vaccine for treating early-stage breast cancer. By designing a larger Phase II trial that included multiple arms, his team identified patients with lymph node involvement as the most appropriate patient population to target in a Phase III trial. This larger Phase II trial dataset also supported using disease-free survival as a trial end point and demonstrated the importance of optimal dosing for vaccine efficacy.

James Gulley (National Cancer Institute) showed compelling data from clinical trials involving a poxviral-based therapeutic vaccine for prostate cancer. His data strongly suggested that this vaccine was more effective in patients with early-stage disease, a finding that should be considered when designing future trials. It is also notable that vaccine-treated cancer patients often showed improvement in overall survival, but not in progression-free survival. This point was reiterated by Kevin Shannon (US FDA), who discussed the FDA's recently published 'Guidance for Industry: Clinical Considerations for Therapeutic Cancer Vaccines' [1]. Cancer vaccine trials should not be abruptly abandoned for failing to show improvement in progression-free survival, as patients may still be found to have significantly increased overall survival. This also highlights the urgent need to identify biomarkers that can predict efficacy early on, without waiting until the very end of the trial.

Robert Petit (Advaxis) described several cases in which vaccine study results were affected by factors such as patient age, marital status, HLA type and comorbidities. While it is impossible to control for every potential variable in a clinical trial, he stressed that every effort should be made to keep all trial arms similar, and to exclude patients who are unlikely to respond well to the vaccine. Additionally, Petit pointed out that a thorough clinical history of each patient could help identify appropriate exclusion criteria for future trials. However, while excluding certain patients from clinical trials may increase a vaccine trial's chance of success, it may also affect the vaccine's labeling after regulatory approval and limit its widespread use.

Marty Anderson's (PharmaNet/i3) excellent presentation raised the issue that an overly complicated clinical trial design can be difficult to implement correctly. While this may not be a major concern for large cancer centers that have extensive experience running clinical trials, it is worth considering when designing an infectious disease vaccine trial employing sites in regions with little clinical trial experience. Clinicians should carefully consider collecting subject biomarker data and other information in ways that will not overwhelm site managers, nurses and trial subjects.

Successful implementation of vaccine clinical trials

Several professionals from vaccine manufacturers and contract research organizations described their experiences with the management and day-to-day operations of clinical trial sites. A consistent message from these presentations was that all of the parties involved with carrying out a trial should be included or considered when making key trial design decisions.

Tina Washington and Janet Christoff (Sanofi Pasteur) described their successful management of two high-dose influenza vaccine trials that enrolled thousands of subjects in a very short timeframe. They emphasized that close communication between managers and trial sites was essential to these trials' success. Ann Wouters (Pfizer) stressed the importance of collecting safety data during a vaccine trial, and gave a helpful overview of adverse event reporting and how the decision is made to stop or continue a vaccine trial. Keith Chirgwin's (Merck) presentation emphasized the need to work closely with regulatory agencies throughout the vaccine development process. This is especially important for vaccines, largely because of the need to collect extensive safety data post-licensure.

Another important consideration for conducting clinical trials today is the use of electronic tools for collecting data. Peggy Snowden (Aeras) discussed the use of electronic case report forms, which can greatly facilitate trial data management if used properly. However, she emphasized the need for careful planning before incorporating electronic tools into a vaccine trial design. Linda Deal (ERT) discussed the possibilities and challenges involved with using electronic

patient-reported outcomes. Electronic diaries and other tools can be given to patients to report adverse events and quality-of-life information, but trial subjects must be well trained and comfortable using such devices in order to obtain useful data.

Solutions for the conduct of global clinical trials

Globalization is an important recent development in the area of vaccine clinical trials. This trend has been driven largely by the low per-patient costs of conducting trials in developing regions. In addition, the higher infection rates often seen in these areas allow for smaller trial sizes. On the other hand, these regions present unique challenges because they often lack the infrastructure for conducting large clinical trials.

Pat Fast (IAVI) and Ann Ginsberg (Aeras) described the extensive partnerships that their organizations have created to conduct clinical trials on HIV and tuberculosis in developing countries. Their organizations' efforts have included constructing new clinical laboratories in these regions, as well as reaching out to community leaders and local regulatory agencies to facilitate the vaccine trial process.

Shayesta Dhalla (University of British Columbia) gave an overview of the challenges involved in enrolling subjects for HIV vaccine trials, and highlighted vaccine-induced seropositivity as a major barrier to enrollment. Heather Kelly (OneWorld Health) and Lionel Martellet (PATH) described the difficulties of obtaining informed consent in regions with low literacy and little familiarity with clinical trials. Despite these hurdles, the speakers all stressed that, with proper planning and coordination, vaccine trials can be conducted anywhere in the world.

Conclusion

The World Vaccine Trials Congress 2012 provided a rare opportunity to hear from a diverse group of professionals all working in the area of vaccine trial design and implementation. Conducting vaccine trials is becoming an increasingly complex process that requires careful planning and communication between many parties. However, the presentations at this conference indicated that researchers, clinicians and trial-site coordinators are finding new ways to meet these challenges and to bring many promising new vaccines closer to the clinic.

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Reference

1 Guidance for Industry: Clinical Considerations for Therapeutic Cancer Vaccines. www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/UCM278673.pdf (Accessed 30 May 2012)