Use of Surrogate Markers of Efficacy

Jerry P. Weir
Director
Division of Viral Products/CBER/FDA

Current State of Efficacy Evaluation of Pandemic Influenza Vaccines

- Evaluation of pandemic influenza vaccines will depend upon surrogate measures of efficacy
- Currently, the principal surrogate measure of efficacy is an immunogenicity response in clinical trials - hemagglutination inhibition (HI) antibody titer
- Use of HI as an endpoint is based on data from seasonal influenza vaccines, primarily inactivated vaccines

HI Antibody Titer as an Endpoint for Pandemic Influenza Vaccine Evaluation

- Endpoint criteria based on experience with seasonal influenza vaccines
  - Seroprotection – defined as % subjects with an HI titer > 1:40
  - Seroconversion – defined as % subjects with a minimum 4-fold rise in HI titer (e.g., pre-vaccination HI titer < 1:10 and a post vaccination titer $\geq$ 1:40, or a pre-vaccination titer $\geq$ 1:10 and a minimum 4-fold rise HI titer)
  - GMT increase in HI antibody following vaccination

Challenges in Efficacy Evaluation of Pandemic Influenza Vaccines - 1

- Is it appropriate to extrapolate what we know from seasonal influenza vaccination to pandemic influenza vaccines, particularly the use of HI as an endpoint and the endpoint criteria previously defined?

EMEA – Guideline on Dossier Structure and Content for Pandemic Influenza Vaccine Marketing Authorisation Application

"The criterion of an HI titre of at least 40 IU is based upon the assumption of a correlation with a reduction in influenza-like illness when most of the vaccinated population has some degree of pre-existing immunity against inter-pandemic strains. This may not be valid for pandemic influenza vaccines."

Challenges in Efficacy Evaluation of Pandemic Influenza Vaccines - 2

- Is an HI antibody surrogate (or any antibody surrogate) appropriate for all types of pandemic influenza vaccines?
  - Live attenuated influenza vaccines
  - Recombinant subunit vaccines
  - Vector vaccines

- How do we define the appropriate immunogenicity endpoints that would serve as a surrogate for evaluating pandemic influenza vaccines?

- How do we establish the protective levels associated with newly defined surrogate endpoints and accurately quantify the responses following vaccination?

Potential Surrogate Immunogenicity Endpoints

HI Antibody Response as a Clinical Endpoint for Pandemic Influenza Evaluation

- Advantages as an endpoint
  - HI assays are simple and high-throughput
  - HI assays are validated and reasonably standardized
  - HI antibody titer of 1:40 has been correlated with reduction in influenza-like illness

- Disadvantages/Concerns as an endpoint
  - Some question about whether a 1:40 HI titer is a protective level for all strains of influenza, including pandemic strains
  - Would a 1:40 HI titer provide similar protection in a naïve population?
  - Does a 1:40 HI titer correlate with protection if assay changes are necessary to achieve sensitivity for pandemic vaccine response (e.g., horse red blood cells)?
  - Is a 1:40 HI antibody titer necessary, if other (potentially more appropriate) surrogates identified?

Neutralizing Antibody Response as a Clinical Endpoint for Pandemic Influenza Evaluation

- Advantages as an endpoint
  - A measure of function thought to be important for protection
  - Neutralization assays are sensitive compared to HI
  - Efforts are underway to standardize

- Disadvantages/Concerns as an endpoint
  - No specific neutralizing antibody titer has been correlated with reduction in influenza-like illness
  - Difficulties in standardization and variability between labs
  - How will protective neutralizing titers be bridged to HI titers and/or protection?

Mucosal Antibody Response as a Clinical Endpoint for Pandemic Influenza Evaluation

- Advantages as an endpoint
  - Mucosal immunity is thought to be important for protection
  - Some studies (e.g., seasonal LAIV) have correlated mucosal antibody (IgA) in nasal washes with protection
- Disadvantages/Concerns as an endpoint
  - No specific IgA antibody titer has been correlated with reduction in influenza-like illness
  - How will protective mucosal antibody titers be determined?
  - Technical difficulties in standardization (e.g., variability of nasal washes)

Cell-Mediated Immunity Responses as a Clinical Endpoint for Pandemic Influenza Evaluation

- Advantages as an endpoint
  - Cell-mediated immunity (CMI) is a likely contributor to protection
  - CMI may provide some degree of cross-protection
- Disadvantages/Concerns as an endpoint
  - No specific measure of cell-mediated immunity has been correlated with reduction in influenza-like illness
  - How would an appropriate CMI endpoint for pandemic influenza vaccine evaluation be defined?
  - Technical difficulties in developing validated and standardized assays
  - Relevance of assays and clinical samples to functional mechanisms?

Potential Attributes of a Useful Surrogate Immunogenicity Endpoint for Pandemic Influenza Vaccine Evaluation

- A correlation of the immunogenicity endpoint with protection in relevant animal models
- A correlation of an analogous surrogate immunogenicity endpoint with protection against seasonal influenza strains in clinical trials
- A correlation of the immunogenicity endpoint in vaccine trials with protective levels measured in subjects following natural infection?
- Availability of validated assays that are practical, quantifiable, and can be standardized among various laboratories

The Role of Animal Models in Defining Relevant Surrogate Immunogenicity Endpoints for Pandemic Vaccine Evaluation

- Strengths
  - Animal model studies can provide an important proof of concept for identifying potential correlates of protection and vaccination strategies
  - Correlate immunogenicity with protection (defined per model)
  - Determine protective levels of an identified marker
  - Facilitate development of an appropriate assay for quantifying the protective level of the identified marker

- Weaknesses
  - Differences between animals and humans (e.g., inbred populations, physiology of influenza infection, etc.)
  - Relevance of animal model to clinical studies?
    - Are protective levels in a model the same as for humans?
    - Is the same thing being measured in the model as in the clinic?

Extrapolation of Surrogate Endpoints Defined in Seasonal Influenza Vaccine Studies to the Pandemic Situation

- Strengths
  - The current surrogate marker (HI antibody) seems to be appropriate and applicable for all currently circulating strains (H1N1, H3N2, and B) and these influenza subtypes were “novel” at one point (e.g., H3N2 – 1968)
  - Establishing new surrogate markers for protection may be feasible only for seasonal influenza strains
  - Seasonal vaccines might provide support for new vaccination strategies (e.g., adjuvants) to demonstrate cross-protection and disease protection for special populations (e.g., elderly)

- Weaknesses
  - Seasonal studies are conducted in non-naïve population unlike those exposed to a pandemic strain
  - How certain are we that an identified level of protective immunity for a given marker is the same for all influenza subtypes?

Studies of Natural Infection as a Guide to Defining Relevant Surrogate Immunogenicity Endpoints for Vaccination

- Strengths
  - The human immune response to infection with novel strains of influenza may shed light on protective mechanisms and levels of specific surrogate endpoints needed for a successful vaccine
- Weaknesses
  - Recovery from infection likely involves multiple mechanisms and distinguishing relative protective effects probably difficult
  - Assumption that recovery means protection may not be true
  - Timing of analysis may limit usefulness of data collected

Development and Evaluation of Assays for New Surrogate Immunogenicity Endpoints

- Assays for a proposed surrogate immunogenicity marker must be appropriate for that endpoint
- Must be robust enough for evaluation of large scale clinical trials
  - High-throughput
  - Quantitative
- Ideally could be applied to animal models as well as in a clinical setting
- Should be standardized with a low inter-laboratory variability so that results of multiple clinical trials can be compared

Advantages to Defining New Surrogate Immunogenicity Endpoints Now

- Guide the development of new/improved vaccines for pandemic influenza
- Increase our confidence in the effectiveness of pandemic influenza vaccines before a pandemic occurs
- Guide development of vaccination policy

Summary and Conclusions

- New surrogate immunogenicity endpoints are needed for evaluating pandemic influenza vaccines
  - Increase our confidence in the effectiveness of vaccines against novel strains of influenza
  - Facilitate development and evaluation of new-generation influenza vaccines
- There are unique challenges to identifying new surrogate immunogenicity endpoints and establishing the levels necessary for protective immunity with pandemic influenza vaccines
- Situations can be envisioned in which there are multiple accepted surrogate immunogencity endpoints, tailored for evaluation of specific types of vaccines
- New or improved assays capable of quantifying such endpoints will likely need to be developed and standardized

Panel Exercise

- Assume that neutralization is a likely surrogate for effectiveness of a inactivated pandemic influenza vaccine containing HA
- What combination of pre-clinical studies, clinical trials, and assay development and validation would be needed to 1) establish neutralization as an acceptable endpoint for evaluating trials inactivated pandemic influenza vaccines, and 2) render it practical and useful for doing so?