Developing Rabies Monoclonal Antibody Products as a Component of Rabies Post-Exposure Prophylaxis: Draft Panel Questions

Abstract:
The focus of this workshop is to discuss the challenges and identify additional scientific work needed to advance development of monoclonal antibodies (mAb) targeting rabies viruses for use in a post-exposure prophylaxis (PEP) regimen, to be used in conjunction with licensed rabies vaccine.

First Panel Session: Animal models, Serologic Assays

Moderators: Damon Deming, PhD and Christine Fehlner-Gardiner, PhD

A primary goal in development of a rabies virus mAb for use as the passive-immunization component of PEP is to assess benefit: to demonstrate that it adds to protection provided by other components of PEP such as wound care and vaccine, while avoiding unacceptable loss of benefit compared with already available hyperimmune globulin products. Clinical efficacy trials may be difficult to interpret and have limitations such as inability to capture the diversity of potential rabies virus strains, transmission routes, and clinical scenarios in which mAb-containing PEP may be used. Animal models and cell culture-based neutralization assays (e.g., RFFIT) can play a critical role in exploring issues such as breadth of activity against different rabies virus strains, barriers to resistance, and relative roles of various factors (e.g., viral inoculum and strain, different components of PEP, individual components of multi-mAb cocktails) that might contribute to outcomes. This panel session will focus on such studies and how they might help to inform the initial clinical evaluation of rabies virus mAb products in adults and children with suspected rabies virus exposure.

1. What can be learned from different animal models about the potential contribution of mAb products? In your discussion, please consider issues such as
    a. the breadth of coverage against diverse rabies virus strains
    b. the potential for rabies virus to escape neutralization
    c. the contribution of the rabies virus mAb product to PEP activity
    d. the contribution of individual mAbs (in a mAb cocktail) to PEP activity
    e. the selection of mAb dosing regimens for initial clinical evaluations

2. What are the strengths and limitations of serologic assays (e.g., serum neutralizing activity assessed by RFFIT) that might help in understanding passive protection during the first few days of PEP before meaningful vaccine response is seen and in assessing immunoglobulin effects on the vaccine response?

3. How can animal data, and serological data from trials enrolling non-rabies-exposed healthy volunteers, help to support initiation of clinical trials in suspected rabies virus exposure? In your discussion please consider issues such as
    a. breadth and initial time course of neutralizing activity in serum after antibody administration
    b. later effect of mAbs on vaccine response
    c. comparisons to available passive-immunization products for both quantity and quality of responses
    d. research gaps to be filled

Second Panel Session: Clinical Trial Considerations

Moderators: Sarah Connelly, MD and George Siberry, MD, MPH

Clinical development of a rabies mAb for use in PEP aims to demonstrate sufficient benefit for use as an alternative to existing hyperimmune globulin products; however, there are challenges in conducting clinical trials in this area. While non-rabies-exposed healthy volunteers can provide some information about neutralizing activity in serum after antibody administration, the relation to protection against disease when used after rabies exposure may not be straightforward. A trial with a placebo-only control group would not be ethical in the setting of rabies exposure. Because of the many factors contributing to non-development of rabies after PEP for suspected exposure, absence of rabies may not indicate the effect of the passive-antibody component. This panel session will focus on clinical trial designs, ethical considerations, and measurements that might aid in understanding whether a new rabies mAb product provides early protection prior to vaccine response, while not increasing vaccine interference.

1. What are the important ethical considerations when designing clinical trials of a rabies virus mAb-based PEP product as an alternative to available hyperimmune globulins?
    a. What are the important ethical considerations in conducting therapeutic trials for rabies virus mAbs in children since children are a vulnerable population at a greater risk for rabies exposure from rabid animals (e.g., dog bites)?

2. Discuss what can be learned from a range of possible clinical trial designs (such as randomized placebo-controlled factorial designs in healthy volunteers, randomized active-control designs in presumptive rabies exposure, and any other designs that might be feasible, ethical, and informative). In your discussion, please consider issues such as
    a. geographic differences in rabies animal vectors and virus strains
    b. standard of care rabies PEP regimen differences (such as different vaccines and mode and timing of vaccine administration)
    c. trial site capabilities (e.g., ability to test animals for rabies virus, obtain timely blood samples for serologic measurements during the early time period when passive immunity is most important prior to vaccine response, and follow patients for possible late-onset disease as well as time course of vaccine response)
    d. interpretability and generalizability of results across different populations at risk

3. In clinical trials, what can be learned from measurements such as serum neutralizing assays regarding the contribution of rabies mAb to the PEP regimen? In your discussion, please consider issues such as
    a. informative time points for sampling both during the early time period before vaccine response and later to assess interference with vaccine response
    b. interpretation of results from both rabies-exposure settings and non-exposed healthy-volunteer settings, with appropriate comparators for each
    c. nature and strength of evidence supporting relationship to clinical benefit