Human Vaccines 6:5, 368-372; May 2010; © 2010 Landes Bioscience

Human Vaccines: News

Court finds no Vaccines-autism link

A federal court has determined that the theory that thimerosal-containing vaccines cause autism is "scientifically unsupportable," and that the families of children diagnosed with the condition are not entitled to compensation.

According to three special masters in the US Court of Federal Claims, the families of Jordan King, William Mead and Colin Dwyer did not prove a link between the vaccines and autism.

Although Special Master George Hastings was sympathetic with the King family and believed they brought their claim in good faith, he found that: "The opinions provided by the petitioners' experts in this case, advising the King family that there is a causal connection between thimerosal-containing vaccines and Jordan's autism, have been quite wrong."

Special Master Patricia Campbell-Smith expressed doubt that the amount of inorganic mercury deposited in the brain from the vaccines could cause the effects the Mead family had alleged. In her report she wrote: "Inorganic mercury is not the form of mercury understood to be most toxic in the doses involved in childhood vaccines, and a normal fish-eating diet by pregnant mothers produces a greater source of inorganic mercury for deposition in the brain than thimerosal-containing vaccines do."

The special masters' decisions are subject to review by judges in the US Court of Federal Claims. The attorneys for the families announced that they will ask the claims court judges to review the decisions and rule that the children are, in fact, entitled to compensation.

"All three families are committed to following the appeals process, and pursuing that avenue to get justice and compensation for their kids," said Tom Powers, lawyer for the families involved.

The three test cases represented thousands of children who have autism and whose parents contend that their disorder was triggered by an early childhood vaccination. Indeed, results of a recent survey published in the journal *Pediatrics* (2010, 125:654-9) showed that a quarter of parents indicated they believe vaccines can cause autism. However, they were surveyed more than one year before the *Lancet* decided in February 2010 to retract Andrew Wakefield`s controversial study linking vaccines and autism.

EU approves Novartis Menveo®

Just a few weeks after gaining approval from the US Food and Drug Administration (FDA), the European Commission (EC) granted a marketing authorization for Novartis' Menveo®, the first quadrivalent conjugate vaccine for the prevention of meningococcal disease, in all 27 European member states.

Marketing authorization was based on data from a pivotal Phase III clinical trial and a non-inferiority study, published last year in *The Pediatric Infectious Disease Journal* (2009, 28:86-91).

Meningococcal disease is a major cause of bacterial meningitis and sepsis with high consequent disability and mortality rates worldwide. The vast majority of all meningococcal disease cases around the world can be attributed to five serogroups of *Neisseria meningitidis*. Dominant groups of meningococcal disease can vary by country and region, and can change over time, making it an even more unpredictable disease.

Menveo vaccine protects against four of the five major bacterial groups responsible for meningococcal disease (*Neisseria meningitidis* groups A, C, W135 and Y) and is indicated for the active immunization of adolescents (from 11 years of age) and adults. The vaccine has been administered to more than 18,500 people and is currently in multiple additional Phase III clinical studies in infants and toddlers worldwide.

"Marketing approval for Menveo for people ages 11 and older is the culmination of 10 years of dedicated effort by Novartis Vaccines to provide a vaccine that can help protect against meningococcal disease," said Andrin Oswald, Division Head of Novartis Vaccines and Diagnostics. "Our priority is to advance the fight against meningitis through innovative vaccines that help save lives."

Menveo was developed using conjugate technology, pioneered by Novartis Vaccines in the development of its meningococcal group C conjugate vaccine, Menjugate®. The polysaccharide antigens, the key components of the vaccine that prompt the body to respond to infection, are attached individually to a carrier protein in order to enhance the body's immune response to the vaccine. Menjugate® has been approved outside the US since 2000 for use in individuals from 2 months of age through adulthood, and is one of the meningococcal group C conjugate vaccines that is responsible for the significant reductions in the incidence of meningococcal group C disease in UK. Novartis also produced MenZB®, a vaccine against a strain of meningococcus B specific to an outbreak in New Zealand.

In addition to Menveo, Novartis is developing a recombinant protein vaccine with the potential to provide broad coverage against multiple strains of serogroup B, the last of the five major disease-causing groups, for which no vaccine is currently available.

Vaccination beats back viral hepatitis

According to a recent report from the US Centers for Disease Control and Prevention (CDC), decades of vaccination campaigns and prevention efforts show promising progress against hepatitis viruses. There has been a decrease of hepatitis A infections in adults, a big drop in hepatitis B infections in people aged 6–39, and a slide in hepatitis C cases in the group considered most at risk.

The CDC researchers tracked individuals' levels of antibodies to various hepatitis sviruses, as a measure for exposure to the particular pathogen, either through infection or vaccination.

The study found that since the late 1980s, there has been a significant increase in the number of US-born American children and teens with anti-hepatitis-A antibody and a decrease in the number of adults aged 40+ with the antibody. According to the CDC experts, these trends likely result from increased immunity in children due to vaccination and a resulting decrease of hepatitis A virus (HAV) exposure and infection among adults.

The investigators also found that hepatitis B virus (HBV) infection among people aged 6-39 significantly decreased in recent years as a result of vaccination programs. According to the CDC, over 90 percent of US children had received at least one dose of hepatitis B vaccine by 2003–2006.

The rate of hepatitis C virus (HCV) infection, notwithstanding that there is no hepatitis C vaccine, is decreasing among people at highest risk of infection, possibly due to prevention programs that target risky behavior such as injection drug use, the researchers noted. The peak age of HCV infection changed from 30 to 39 years during 1988–1994 to 40 to 49 years during 1999–2008.

Viral hepatitis is a major public health concern in the United States and HAV, HBV and HCV are the three most important types of hepatitis. HBV and HCV can both trigger chronic infection that can progress to liver disease, cirrhosis and cancer. With 70-85 percent of people acutely infected becoming chronically infected, HCV is the most common chronic blood borne infection in the US and thus a major target for vaccine and drug developers.

FDA fast track status for IMVAMUNE

Recently, the currently unlicensed smallpox vaccine IMVAMUNE® has gained fast track status at the US Food and Drug Administration (FDA). Pivotal Phase III studies will be initiated in 2010.

The Denmark based company Bavarian Nordic, an international leader in the field of smallpox vaccines, has recently received notification that the FDA has accepted all the actions taken by the company to address the observations made during the inspection of the manufacturing facilities in 2009. This was the last step along with the clinical and preclinical data that will be used to potentially support the use of IMVAMUNE® following a declared emergency.

"This conclusion from the FDA concerning our manufacturing process, as well as the data submitted in support of IMVAMUNE® to date, marks a major milestone for Bavarian Nordic, as we now complete the transformation into a fully industrial biotech company," said Dr. Anders Hedegaard, President and CEO of Bavaria Nordic. With a full order sheet for the coming years, we are well positioned for future growth and success."

IMVAMUNE® is the company's third-generation smallpox vaccine and is derived from the parent strain Modified Vaccinia virus Ankara (MVA), which is a highly attenuated poxvirus that has lost the capacity to replicate in human cells, hence solving the main safety issue of conventional vaccines. Although IMVAMUNE® is currently an unlicensed vaccine, it is already in production and available for governments globally under their national emergency rules.

A new study published in the journal *PLoS One* (2010, 5: e9659) provides additional efficacy data supporting the post-exposure protection provided by IMVAMUNE®, which is one of the requirements to potentially support the use of this vaccine following a declared emergency. The study authors demonstrated that mice could be protected from a lethal infection with mousepox, a closely related virus to smallpox in man, by treating the animals with a single vaccination with IMVAMUNE® three days after the animals had received the lethal infection. They further provided insight into the mechanism of protection, which is one of the requirements for future licensing of IMVAMUNE® as a smallpox vaccine for the general public in the US.

Longer needles for obese vaccinees

A new vaccination study shows that needle size does matter for obese people. US researchers found that using a standard 1-inch needle to immunize obese adolescents against hepatitis B virus produced a much weaker immune response than using a longer needle.

"As obesity rises in the US, we need to be aware that the standard of care may have to change to protect obese youth," said study co-author Dr. Amy Middleman from Baylor College of Medicine in Houston, Texas.

Over three years her team vaccinated 22 young women and 2 young men in the shoulder, randomly assigning them to be injected with either a 1-inch or a 1.5-inch needle. The two groups turned out to have different antibody counts depending on the needle used. In those injected with the short one, the number was almost halved. The study was recently published in the journal *Pediatrics* (2010; 125:e508-e512).

Although everyone in the study had enough antibodies to be considered protected against hepatitis B, a lower count generally means a less robust response. "It gives us more evidence of the importance of choosing the right needle length, because we just don't know what the impact could be in other vaccines" said Middleman.

For years, doctors have known that vaccines tend not to work as well in heavy people, but it was unclear whether the obese have weaker immune systems, or fat keeps shorter needles from reaching muscles, where the vaccines can affect immune cells.

The introduction of the hepatitis B vaccine in the 1980s offered some clues. Dr. Gregory Poland from the Mayo Clinic in Rochester, Minnesota told Reuters Health that initially the shot was given in the buttock, but was found to fail to protect some female nurses. Instead of entering the muscle as it was supposed to, the vaccine apparently was broken down in the fat tissue, where it had little chance to stimulate immune cells, and so doctors began giving the shot in the less-padded shoulder.

With the obesity epidemic now adding extra insulation to the shoulder, "our needles are going to have to be longer," Poland said.

The Centers for Disease Control and Prevention recommends longer needles in obese patients, but it is unclear how many doctors follow these guidelines, or even know about them.

Dr. Middleman cautioned that there is no need to be overly concerned until more research has been done.

Species neutral correlates of immunogenicity for vaccines and protein therapeutics

Fact or science fiction

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Much like the humanoid Na'vi in the movie *Avatar*, "species neutral" correlates of immunogenicity have been a hot topic at recent conferences such as the ASM meeting on biodefense (Baltimore, February 18, 2010). While it might seem that developing "species neutral" measures of immune response is critically important for the development of better vaccines and safer therapeutics, like the Na'vi, the concept is closer to science fiction than many would hope.

First, some definitions. What is "species neutral"? From the perspective of vaccination and immunogenicity of protein therapeutics, "species neutral" relates to models that will mimic the progression and kinetics of an immune response regardless of the host species. Similarly a "species neutral" correlate is an indicator of an immune response that is not unique to a host species. For example, antibody titers following immunization or exposure have traditionally been considered species neutral because it has been assumed that if antibodies are generated in the animal model, they will be generated in a natural, human infection.

The hope is that such models could be used to improve the accuracy of pre-clinical immunogenicity studies, allowing drug (and vaccine) developers to identify a set of clinical correlates that will drive products' progress more rapidly towards approval. After all, what could be better than a simple "correlate of immunogenicity" assay that could move directly from pre-clinical (murine, non-human primate) into the clinic?

As is often the case, fact is more complicated than fiction. There was considerable debate on the subject at the recent ASM biodefense meeting and discussion about why immune responses in animals might not reflect immune responses in humans. The problem is that purported species neutral measurements of immune responses such as antibody titers, and measurement of cytokine ELISA's may not reflect the immunological determinants that trigger or support the development of the immune response. To be more specific, measurement of antibody or even cytokine response across different species may be easy to do in a species neutral manner but the immunological determinants of titer or cytokine response are likely to be different between species. For example, whilst T-cell responses can be stimulated in different host species against the same protein, the T-cell epitopes (immunological determinants) that are presented to the immune system in each host are likely to be different. The immunogenic T-cell epitopes are determined by factors including MHC restriction which is unmistakably species specific.

Thus "correlates" (of immunogenicity and protection) are dependent on "determinants" and determinants are not species neutral. A correlate is just that—a measure of immune response, and it is not necessarily linked to a shared determinant between species. A determinant is an aspect of the antigen or immune response that contributes directly to the immune response—such as the T-cell epitopes contained within the sequence of the antigen, or the breadth of T-cell response, or the B cell response, or the antibody isotype. The distinction between correlates and determinants is an important one for drug developers. Regulators often request correlate data without regard to the actual immunological determinants.

For example, the titer of IgG response is the result of a complex cascade of events, which are influenced by a variety of immunological determinants. One of the most important determinants upon initiation of this cascade is the nature of the antigen which in many instances dictates the type of immune response.[1] As the immune response develops it is ultimately the cross-talk between B and T cells (driven by B/T cell epitopes in/on the antigen, respectively) that will affect the specificity, isotype, affinity and longevity of the humoral response.[2] Characterization of factors that influence an immune response requires an understanding of the key immunological determinants as well as measuring the final outcome of an immune response e.g., IgG titer.

Since there is an absolute requirement for T cell help in order to stimulate a high affinity antibody response with -cell memory,[3] it is important to assess the strength of the signal delivered by T-cells. This can be achieved by measuring the quality as well as the quantity of the T-cell response which will ultimately determine the type and strength of the humoral response. Indeed, since measuring B-cell epitopes in proteins is notoriously difficult there has been considerable effort made to accurately measure T-cell epitopes in protein sequences.[4] Unfortunately, measurement of T-cell epitopes in animal models does not always translate to humans, mainly due to the differences in species' MHC which affect the repertoire of T-cell epitopes presented. This also applies with closely related species such as human and non-human primates,[5,6] and MHC restriction can even be a factor when comparing responses among individuals of the same species.

The repertoire of MHC alleles in the human population is incredibly diverse. The highly polymorphic nature of the human MHC locus results in subtle differences in the binding pockets of MHC molecules in humans and this can be the difference between one patient's body rejecting therapy while another's accepts it.[7,8] The importance of MHC alleles in underpinning immune responses is exemplified by the fact that different MHC alleles within a single species can be correlated with either an increased or decreased risk of various autoimmune and infectious diseases,[9-11] this fact alone limits the utility of modeling immune responses in different species (that express unrelated MHC molecules).

Since correlates depend on determinants, what methods exist for measuring the determinants of immunogenicity? T-cell response can be predicted using silico immunogenicity screening, in vitro screening using naïve blood donors or exposed subjects,[8] and in vivo screening using HLA transgenic mice.[12-14] While there has been tremendous success in using each of these techniques, caveats remain. In silico screening

of autologous proteins has to be carefully calibrated due to the presence of two types of epitopes (regulatory and effector, see reference 15). In vitro screening with "naïve" blood may give a skewed estimate of immunogenicity due to the effects of heterologous immunity, the process by which exposure to one antigen primes the immune system for a response to another, possibly unrelated, antigen.[16] In vitro culture does not accurately reflect the dynamic cross-signaling that may occur in three dimensional structures, although new culture systems are attempting to replicate that complexity in vitro.[17,18] And in vivo studies, carried out using HLA transgenic mice, are hampered by the expression of only a single HLA (MHC allele) per mouse strain whereas humans have multiple HLA alleles. The new BLT Hu-SCID mice, transplanted with human immune tissue, may overcome this problem but the method promises to be tedious as each mouse is carefully crafted by hand.[19]

What's the take home message? Unfortunately, until we can find animals that are transgenic in a way that reflects the diversity and complexity of human HLA, it is likely that "species neutral" models will remain elusive. A single protein may contain multiple HLA "motifs", or may contain none, and the number of HLA motifs may be completely different from the number of MHC motifs for the selected animal model. Having more or less motifs in the candidate antigen will lead to more or less immunogenicity and differences between species. Measures of immune response like antibody titers and gamma interferon ELISAs are determined by T cells, and while they may be "correlates", the statistician's mantra "correlation does not equal causation," still applies. One must remember that measurements—or correlates—reflect determinants, which differ from species to species. The concept that a determinant of immunogencity might ever be "species neutral" is really just like the Na'vi: a science fiction fantasy.

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