

Addendum to Citizen's Petition Docket # 02P-0349/CP 1 filed on August 5, 2002

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Dockets Management Branch
Food and Drug Administration
Department of Health and Human Services
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I have enclosed some additional information for the FDA to consider when reviewing Citizen's Petition Docket # 02P-0349/CP 1, filed on August 5, 2002.

I have one additional point regarding an action:

Additional Action requested

* The product insert of the hemophilus vaccines should provide information to the prescriber that there appears to be a dose response between the number of doses of vaccine given and the development of IDDM.

Additional information

Data from a large prospective clinical trial supports a causal link between the hemophilus vaccine and type 1 diabetes, IDDM, in humans. In that study we found clusters extra cases of IDDM starting approximately 38 months after immunization and lasting about 6 months (1). These findings are made even more credible by data showing clusters of cases of IDDM occurring 2-4 years after mumps infection and data showing a 2-4 year delay between the development of antipancreatic autoantibodies and the development of IDDM.

02P-0349

SUPI

I had previously informed the FDA that there have been papers published by several different groups of authors which reported clustering of cases of IDDM occurring 2-4 years after infection with mumps virus (2-5). Sultz et al. (2) published epidemiology data that there was a 3 to 4 year delay between mumps epidemics and IDDM epidemics. The authors described a median lag time of 3 years and a mean lag time of 3.8 years between the infection with mumps and the development of IDDM. A group from Finland reported a 2-4 year delay between mumps infection and the development of IDDM (3). The authors also cite two older publications which reportedly contain a similar delay between mumps infection and the development of IDDM (4,5).

I also want to inform the FDA about studies following the progression to IDDM in patients with autoantibodies directed against pancreatic islet cells. Centers in many different parts of the world have prospectively followed the progression to diabetes in individuals with one or more autoantibodies. The delay between the detection of autoimmunity and the development of IDDM is very consistent between centers when looking at similar groups. The studies that are most analogous to the cases of vaccine induced diabetes are in groups of people that have been prospectively followed prior to the development of autoantibodies. In these studies the median onset of diabetes following the onset of autoimmunity is roughly 3 years. There is also about a 2 year delay between the beginning of autoimmunity and the development of any significant number of cases of IDDM.

Researchers have been prospectively following a group of 765 initially non diabetic siblings of diabetic patients in Finland (6), (7). Diabetes manifested after a mean time of 3.2 years from the detection of anti islet cell antibodies in those that were initially negative at the beginning of the study (6). ICA antibodies had the highest sensitivity of any autoantibody with a sensitivity of 100% and presence of a persistent ICA had a actuarial risk of developing IDDM of 47%. The authors found that ICA antibodies had a lower predictive value in controls from the general population than in the siblings of the diabetics (8) which could indicate that those in the general population, as opposed to the siblings, are more likely to have genes that keep the ICA antibodies from destroying pancreatic islet cells. A second study from Finland, prospectively following 4,590 newborns with high and medium genetic risk for developing diabetes (9). The authors found that 95% of all autoantibodies associated with IDDM, including IAAs, GADAs and IA-2s, the sero-conversion occurred in clusters -12 to 8 months around the time of ICA sero-conversion.

A German study prospectively followed children, at risk for developing diabetes because of family history, from birth. Researchers screened blood at birth, 9 months, 2 years, and 5 years. They found that in children who had two autoantibodies by age 2, 50% developed diabetes by age 5, a median onset of approximately 36 months after detection of autoantibodies (10).

Numerous groups have followed the progression to diabetes in high risk patients who have one or more autoantibodies present at the time of enrollment into the study. The median or

mean progression time is often near 3-4 years. A group in Finland followed 701 individuals at high risk for IDDM, mean age of 9.9 years. The authors found the median time between the enrollment in the study and the development of IDDM was 3.3 years while the median follow up time for the non progressors was 10.3 years (7). Almost all of those who were ICA positive at the beginning of the study, and went on to develop diabetes, did so within 5 years. A large US study (11) followed 7,834 high risk people (median age 27.4 years) for the development of IDDM, with a median of 4.6 years of follow-up. During the study 135 participants developed IDDM with a median age 10.5 and a median time between the enrollment in the study and the development of IDDM of 2.8 years, similar to the Finnish study above. An group in Italy (12) followed 158 individuals, median age 45, with islet cells antibodies (ICAs) for the development of IDDM. The mean time between the enrollment in the study, ICA positive, and the development of IDDM was 4.8 years. The investigators looked at factors associated with faster progression to development of IDDM in autoantibody positive individuals. They found those with a family history of IDDM, family history of other autoimmune diseases and a younger age may progress to IDDM quicker than others who have the same autoantibodies at the time of enrollment in their study.

The similarities in temporal delay between either infection or immunization and the onset of IDDM compared to the progression of autoantibody positive patients to develop IDDM may be explained by the ability of infections and vaccines to induce the development of autoantibodies. Natural infections with mumps has been linked to the development of islet cell cytoplasmic antibodies (ICA autoantibodies) (13,14) Immunization at birth with BCG vaccine has been associated with decreased risk of diabetes in humans (15) and has recently been associated with a decreased GAD65 and IA-2 autoantibodies (16). The hemophilus vaccine, which has been shown to cause diabetes in humans (1), was evaluated in a case control study using autoantibodies in high risk children (17). While the case control study was small and the results were not statistically, the odds ratio were similar to that seen in the clinical trial with the hemophilus vaccine (1). Islet cell autoantibodies also were found to develop in 3 of 239 10-year old girls following rubella vaccination (18). Furthermore vaccine can cause diabetes in NOD mice, an animal model of IDDM (1). Autoantibody titers especially with antibodies to insulin are strongly associated with the development of IDDM (19).

The 2 year delay between infection or immunization and the development of the cluster is consistent with a progressive autoimmune disease. The data suggests that in most individuals with a healthy pancreas it would take at least two years for autoimmunity to destroy enough islet cells for the person to become diabetic. In older groups containing individuals whose beta cells may have been partially destroyed by prior insults it would be expected that some individuals would develop diabetes soon after immunization or infection. Support for this theory is supplied by data from a US study which followed the development of IDDM in autoantibody positive patients. Over 90% per cent of patients who had an abnormal glucose tolerance at the time of enrollment in the study developed diabetes by 6 years compared to about 55% who had a normal

glucose tolerance at the beginning of the study (20). This may explain our epidemiology data which indicated the Hepatitis B vaccine was associated with rises in the incidence of IDDM starting about one year after immunization (15) in New Zealand.

There are likely many cases of vaccine or infection induced IDDM where the onset of diabetes occurs more than 4 years after immunization. In an analysis of an hemophilus vaccine clinical trial there were an extra 6 cases/100,000 that occurred between ages 7-10 in the group receiving the booster dose of Hemophilus vaccine at age 2 years of age compared to the control (1). These extra cases of IDDM occurred after the cluster. Prospective studies of autoantibody positive patients shows that while most of the patients who progress to IDDM do so before 5 years there are patients who progress to IDDM up to 10 years later (6,7,11,12). These findings are consistent with a delayed, or slowly progressive autoimmune disease, which appears more commonly in studies of older individuals. These findings are also consistent with blood tests showing many older individuals initially diagnosed by Type II diabetes have autoantibodies to their islet cells and actually have an latent autoimmune, Type I diabetes. These individuals often require insulin years after their initial diagnosis (21,22). It is not known why older individuals are likely to have a more slowly progressive disease. Data indicates individuals with the high risk genes develop a rapidly progressive autoimmune disease resulting in IDDM very early in life while others who have moderate risk genes have a slower progressive autoimmune disease and develop IDDM later in life (9). In the later case the autoantibodies may be less cytotoxic the islet cells or the islet cells may have enhanced repair mechanisms to protect the islet cells.

There may be differences between the ability of vaccines to induce IDDM and natural infections (23) Vaccines often contain aluminum and other ingredients which differentiate them from natural infections. Immunization with killed vaccines instantaneously exposes the immune system to a large bolus of immunogens intramuscularly while with natural infections the body is gradually exposed to increasing amounts of immunogen as the organism crosses the mucous membrane and divides. Another difference between natural infections and vaccines is that exposure to natural infections occurred for hundreds of generations prior to the existence of insulin therapy. This would have allowed natural selection to take place and the genes for susceptibility to diabetes, following natural infections, to be removed from the gene pool. This would explain why studies in some populations have found an infectious agent to be diabetogenic and in other populations the agent is not. This could explain discrepancies in studies showing effects and lack of effects by coxsackie viruses.

I hope the additional information will help the FDA in making its decision on the previously filed Citizen's Petition.

Sincerely,


John B. Classen, MD

9/3/02

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446