Vaccination and Autoimmune Diseases: the Argument Against

Ethan Rubinstein MD
Department of Infectious Diseases, Sheba Medical Center, Tel Hashomer, Israel
Affiliated to Sackler Faculty of Medicine, Tel Aviv University, Ramat Aviv, Israel

Key words: vaccination, autoimmune diseases

Vaccines against infectious diseases have been alleged to cause autoimmune phenomena. Certainly such phenomena, e.g., autoantibodies, including those to autoreactive T lymphocytes, may develop secondary to various vaccines. Nevertheless, autoimmune diseases secondary to vaccines against infectious diseases have occurred very rarely in the past and probably not at all with current vaccines (excluding the recently employed but long-ago produced smallpox vaccine).

To diagnose a vaccine-related autoimmune disease the following criteria have to be fulfilled according to the World Health Organization [1]:

- Consistency and strength: autoimmune findings following vaccine administrations should be the same in different patient cohorts, irrespective of the method of investigation and the investigators performing the study, and the associations should be strong.

- Specificity: the association between the vaccine and autoimmune symptoms/findings should be distinctive and specific. The association should not rise spontaneously or commonly with other external stimuli.

- Temporal relation: a clear temporal relation between the vaccine and the adverse event is mandatory; this temporal relation may be considered strong if properly designed and if carefully conducted clinical trials demonstrate the association in a statistically significant manner. The temporal relation needs to be corroborated by randomized clinical trials, cohort studies, case-control studies, controlled case-series analysis but not by case reports. Predisposition of certain populations (elderly, genetically disposed, ethnic, sociological and with specific conditions) to develop such vaccine-associated adverse effects should be defined in such studies.

- Consistent results: by at least one study in different populations by different investigators; different relevant methodologies are necessary.

- A non-random temporal relation between the predefined adverse event and vaccine is necessary and the frequency of the adverse event needs to be significantly different in a vaccinated population as compared to a non-vaccinated non-selected population.

Vaccinal autoimmune diseases
Guillain-Barré syndrome and "swine flu"

While the medical literature is soaked with claims and counter-claims linking autoimmune disease to vaccinations, only in a few rare cases have autoimmune disease been firmly linked to vaccination against infectious diseases in humans. Probably best known is the association of Guillain-Barré syndrome with the swine flu – A/New Jersey/87/6 vaccine that was employed in 1976–1977 in the United States. While the average rate of GBS in the general population and in populations immunized with other influenza vaccines was approximately 1:100,000, the rate rose to 7.6:100,000 during 5 weeks in individuals who had been immunized with the swine flu vaccine [2]. To date, the risk of GBS after influenza vaccine will add an additional case of GBS per 1 million people vaccinated.

Thrombocytopenia following measles-mumps-rubella vaccination

The reported incidence of thrombocytopenia following administration of the MMR vaccine was reported to be 1:30,000. This risk is tenfold lower than that occurring after naturally occurring rubella (1:3000) [3] and fivefold lower than that occurring after naturally occurring measles (1:6000) [4], with patients with preexisting immune thrombocytopenia being prone to the complication – mitigating against the use of this vaccine in such patients.

Hepatitis B vaccine and multiple sclerosis

A report from France described 35 cases of young women (average age 30 years) with multiple sclerosis that occurred during a 7 year period following the recombinant hepatitis B vaccine. The disease was diagnosed in half the patients within a 3 year period. This report raised considerable concern [5]; further investigation of this group found an over-representation of HLA-DR2 antigen and a strong family history of multiple sclerosis. In the ensuing years, 25 million French people received the vaccine and several hundred cases were reported to the French pharmacovigilance agency. Twelve subsequent studies, 2 of them with a very large number of subjects, failed to establish an association between hepatitis B vaccine and demyelinating disease [6]. A case cross-over European study also failed to establish the alleged association, and the risk of having a relapse of multiple sclerosis was in fact diminished in vaccine recipients in the 2 months following vaccination (relative risk 0.7, 95% confidence interval 0.4–1.26). A nested case-control study in the U.S. of 121,700 women also failed in a multivariate relative risk model to support the association between hepatitis B vaccination and multiple sclerosis, the relative risk associated with hepatitis B vaccination in the last 2 years and the new onset of multiple sclerosis being 0.7 (95% CI 0.3–1.8). In the interim,

GBS = Guillain-Barré Syndrome
MMR = measles, mumps, rubella
CI = confidence interval

IMA J • Vol 6 • July 2004
Vaccination and Autoimmune Disease 433
500 million people in 25 countries were immunized with the hepatitis B vaccine without significant adverse events (6).

Diabetes mellitus
In recent decades there has been a significant increase in type 1 diabetes around the world, and childhood vaccines have been incriminated as a possible trigger. While a case-control study did not identify this association (7), the timing of vaccination with Haemophilus influenzae type B (to children 2 months and older) could be associated with an increased incidence of type 1 diabetes (8). Nevertheless, a study in 100,000 Finnish children found no increased incidence of type 1 diabetes in children immunized at ages 3, 4, 6, and 14–18 months as compared to children immunized once at age 2 years (9). An additional large study from the U.S. also failed to establish this association (10). The current state of knowledge has not identified any effect of childhood vaccinations on type 1 diabetes.

Smallpox vaccine
Smallpox vaccination following the recent bioterror anthrax attack in the USA has been resumed for military personnel and in 'first responders.' In Israel and the U.S. together, some 55,000 first responders who were previously immunized against smallpox were re-immunized in the U.S. Of 36,217 civilian vaccines 21 cases of myocarditis-pericarditis were reported at a rate higher than expected in non-vaccinees (11). Moreover, in the U.S. an additional 230,734 military first-time vaccinated individuals were screened for myocarditis-pericarditis. Although the rate of myocarditis-pericarditis was 7.8/100,000 in the 30 days following vaccination, the background for this adverse event is presumed autoimmunity – a rate of 3.6 (95% CI 3.3–3.9) higher than expected (12). In addition, a few reported cases of peripheral and central neuritis were also attributed to autoimmunity. These adverse effects were only rarely reported in first-time smallpox-immunized individuals. A re-analysis of cardiac deaths following the 1946–1947 vaccination of some 6.4 million New Yorkers did not disclose excessive cardiac mortality among all age groups (13). The temporal association between the vaccine and these particular effects at a ratio far higher than in a control population raises the possibility of autoimmune disease having been induced by the smallpox re-vaccination program. Nevertheless, specific studies linking autoimmune diseases and smallpox revaccination have not yet been published.

Future vaccines
Obviously, the field of vaccinology is growing fast, and new adjuvants are being utilized that are capable of initiating a strong innate immune response. DNA vaccines, vaccines based on dendritic cells pulsed with tumor antigens, etc., are on the horizon. These vaccines and others still under development may induce strong autoimmunity. Immunologic and molecular mimicry between vaccines and host epitopes need to be identified, because the ability of the introduced antigen to bind to major histocompatibility complex molecules and to be recognized by autoreactive T cells is a real possibility.

A new Lyme disease vaccine utilizing the Borrelia surface protein A displays homology to human lymphocyte function associated antigen-1 (14) and has raised concern regarding possible autoimmune reactivity; however, there was no evidence in clinical trials of increased arthritis frequency in vaccine recipients.

Concluding remarks
Some natural infections cause autoimmune diseases, such as Campylobacter jejuni and GBS (15), herpes simplex keratitis and recurrent chronic keratitis (16), Thelias virus encephalitis in mice (17), among others. In contrast, in vaccines against infectious diseases a single confirmed episode of the swine flu and association with GBS and one suspected episode of smallpox re-vaccination and pericarditis-myocarditis and neuritis have been recognized – both occurring in adults immunized with viral vaccines.

At the present time, no risk for autoimmune disease is associated with vaccines against infectious diseases, particularly with childhood vaccines, short of the smallpox vaccine. Nevertheless, continuous vigilance and epidemiologic investigations are vital to ensure the safety of these vaccines, which constitute the single most important development for reducing mortality.

The value of the vaccines lies in their global acceptance and implementation as the best way to eradicate the big killers like polio, tetanus, diphtheria, etc. Discontinuation of vaccination based on wrong assumptions, false accusations and unbiased claims may cause more harm than good.

References
Research Projects

**Estrogen effects on the generation of T lymphocytes in aging female mice**

F. Kohen¹, D. Somjen² and A. Globerson²

Departments of ¹Biological Regulation and ²Immunology, Weizmann Institute of Science, Rehovot, and ³Institute of Endocrinology, Tel Aviv Sourasky Medical Center affiliated to Sackler Faculty of Medicine, Tel Aviv University, Ramat Aviv, Israel

**Background:** Aging is associated with a decrease in T cell functions and reducing levels of circulating sex steroids. However, the aspects related to a deficiency in sex steroids on thymic function have hardly been investigated. Accordingly, we studied the short and long-term effects of sex steroids and phytoestrogens on the thymus of rodents (mice or rats) during aging.

**Objectives:** To establish new strategies for promoting the generation of T lymphocytes under conditions of sex steroid deficiency (e.g., aging, gonadectomy), consequently improving immunity and immunosurveillance.

**Methods:** Our findings are based on analyses of creatine kinase (CK) response, flow cytometry and western immunoblots.

**Results:** Sex-specificity is not maintained under conditions of sex steroid deficiency in the thymus of female or male animals, but maintained in the reproductive organs (uterus or prostate) with respect to CK response following hormonal treatment with estradiol (E2) or dihydrotestosterone. The CK response to E2 in the thymus could be blocked by tamoxifen or raloxifene, indicating that the response to CK is mediated via the classical estrogen receptor. Four months treatment of ovarectomized rats with E2, raloxifene, genistein or daidzein led to a significant increase in CK activity and progesterone receptor expression in the thymus, but in the uterus only daidzein and E2 caused an increase in CK activity.

**Conclusions:** Our observations suggest that the thymus behaves differently to hormonal manipulation than the endocrine organ during aging.

Supported by the Chief Scientist's Office of the Israel Ministry of Health