Influenza Vaccine and Autoimmunity

Nancy Agmon-Levin MD1,2, Shaye Kivity MD1,3 and Yehuda Shoenfeld MD FRCP1,2,4

1Center for Autoimmune Diseases, and Departments of 2Medicine B, 3Medicine A & C, Sheba Medical Center, Tel Hashomer and 4Sackler Faculty of Medicine, Tel Aviv University, Ramat Aviv, Israel

KEY WORDS: influenza vaccine, autoimmunity, autoantibodies, adjuvant, molecular mimicry

Influenza, commonly known as the flu, is an infectious disease caused by RNA viruses of the Orthomyxoviridae family. The first influenza pandemic was documented in 1580 and ever since has remained a viral disease of global dimension, presenting with annual epidemics and infrequent pandemics [1]. During the Spanish flu pandemic in 1918 the only efficient therapy was transfusing blood from recovered patients to new victims of the virus. Following this observation and the ability to grow the virus in embryonated hen eggs discovered in 1931, the United States military developed the first inactivated influenza vaccine in the 1940s [1]. Currently the advanced-type vaccine, composed of two inactivated viruses – influenza A and influenza B – are used worldwide for the prevention of influenza and its serious complications [2]. Unlike other viral vaccines, the influenza vaccine must be administered every year, and its antigenic profile differs yearly [2]. Current human vaccines are considered safe and effective by the medical community, for the general population as well as for patients with autoimmune rheumatic diseases [3,4]. Nevertheless, post-vaccination adverse events especially those of an autoimmune nature, although rare, have been described.

In the current issue of IMAJ, a case report by Vainer-Mossel et al. [5] describes a 55 year old woman who presented 4 days after receiving an influenza vaccine, with acute confusional state and a middle cerebral artery occlusion detected by magnetic resonance imaging. The patient was concomitantly diagnosed with systemic lupus erythematosus and secondary antiphospholipid syndrome. Thus, an intriguing link between influenza vaccine and SLE/APS-associated diffuse neurological symptoms (i.e., stroke and possible lupus cerebritis) was suggested.

Systemic and neurological autoimmune phenomena have been documented following influenza vaccine. Post-vaccination production of autoantibodies, which had become one of the safety criteria of vaccines, was reported in several studies following inoculation. Abu-Shakra and colleagues [6] evaluated 24 women with SLE who received an influenza vaccine. Antibodies reacting with Sm, Sm/RNP, Ro and La antigens were observed 6–12 weeks following vaccination, and six and three patients developed immunoglobulin G and M anticardiolipin antibodies, respectively. Recently, autoantibody production (i.e., antinuclear antibody, aCL and anti-beta-2 glycoprotein 1) was studied in 92 healthy medical workers after influenza vaccination. For subjects with autoantibodies before vaccination, increased titers were documented 1 and 6 months post-vaccination in 11% and 13% of them respectively. Moreover, four participants developed de novo autoantibodies 6 months after vaccination, one of them with very high titers, alluding to a possible long-lasting effect of the vaccine [7].

In addition to the appearance of autoantibodies, clinical presentations or mild exacerbations of an autoimmune disease were occasionally observed following vaccinations but severe exacerbations were rarely reported [3,8]. Recently, Conti et al. [4] rarely the current literature on the safety and efficacy of the influenza vaccine in SLE patients. In 125 non-active SLE patients who received vaccination, 4 had a flare, but for the group as a whole the vaccine was considered safe. Other studies evaluated the SLE Disease Activity Index post-vaccination and did not observe any increase. In 48 patients with SLE of whom 24 received the influenza vaccine while the other 24 patients were not immunized, SLEDAI at 6 and 12 weeks after vaccination did not differ between the groups. However, within each group the decrease in SLEDAI over time was statistically significant [9]. In another study of 28 SLE patients, 14 received the influenza vaccine. The SLEDAI showed no differences between vaccinated and non-vaccinated patients, but flare-ups were documented in 2 of the 14 vaccinated patients. It was therefore concluded that influenza vaccine is safe for the majority of patients with SLE, though it is not recommended for patients with active disease [9]. Therefore, although most reports could not link the vaccine with SLE presentation or flare-up in a causal relationship, a temporal association was documented, and the debate regarding such an association has not yet been resolved.

Influenza vaccine is also associated with autoimmune neurological diseases such as Guillain-Barre syndrome. A causal relationship between the vaccine and this autoimmune neurological disease was noted in 1976 during an out-
break of Guillain-Barre that was caused by the swine flu vaccine [10]. Following the introduction of the new HA-type of vaccine, these post-vaccination events decreased significantly. Nevertheless, in the New England Journal of Medicine, 74 cases of Guillain-Barre syndrome had been reported until 1996, and a relative risk of 1.7 was calculated [10]. Furthermore, according to the Vaccine Adverse Event Reporting System, 54 reports of post-vaccination Guillain-Barre syndrome occurred in the U.S. in 2004. In 38 of them the disease occurred within 6 weeks and the highest number (n=31) was observed in patients who had been vaccinated [11]. Other neurological autoimmune diseases, e.g., acute disseminated encephalomyelitis or transverse myelitis, have occasionally been reported following influenza vaccine [12-14].

Autoimmune diseases develop in individuals who are genetically susceptible after their immune system is triggered (i.e., by infection or vaccine). Avoiding such a triggering stimulus may allow an individual to remain asymptomatic throughout his or her life [15,16]. The interactions between vaccines and autoimmunity are closely linked to the established association between infections and autoimmunity. Infectious agents can cause or trigger autoimmunity via several mechanisms such as molecular mimicry, polyclonal activation, bystander activation, the presence of super-antigens, etc. [17]. Vaccines, like infections, activate immune mediated mechanisms, thereby inducing a protective immunity. Theoretically, the more complex a vaccine and the more varied its array of infectious antigens, the more likely it is to trigger an immune response that may eventually turn into an autoimmune disease. The most common mechanism by which infections or vaccines induce autoimmunity is molecular mimicry. The infectious/vaccine antigen incorporates an epitope that is structurally similar to a self-antigen and therefore induces self-reactivity. Bystander activation is a situation where enhanced cytokine production promotes the expansion of autoreactive T cells, whose prior number had been insufficient to produce an overt disease. In the case of polyclonal activation of B cells, the increased B cell proliferation, antibody production and the generation of circulating immune complexes may eventually damage self-tissues. Moreover, the increased risk of autoimmunity among recipients of a certain vaccine may stem not only from its antigenic-mediated responses but also from other constituents of the vaccine, such as yeast, adjuvant and preservative. The importance of these components has been known for years, and has been used to improve the safety and efficacy of vaccines. For example, adjuvants have been added to vaccines to improve their immunogenicity. However, alongside their supportive role they were found to themselves inflict an illness of autoimmune nature, defined as "adjuvant disease" [18]. Pristane is an adjuvant that was extensively studied in a mouse model. Intraperitoneal immunization of mice with pristane induced SLE-like immunity documented by the production of autoantibodies and pro-inflammatory cytokines (i.e., interleukin-6, interferon-alpha) [19,20].

In the case reported in this issue [5] the autoimmune manifestations presented 4 days following vaccination. Temporal association of several days might be the result of some immune mediated mechanisms. Molecular mimicry usually requires several weeks following first exposure to an antigen. As prior influenza infection or vaccination can not be excluded, a second exposure to the same antigen might elicit a response within a shorter period. Other mechanisms such as polyclonal activation or an adjuvant effect can also be activated within this time frame. Thus, it might be suggested that in the patient described [5] vaccine administration had increased the titers of antiphospholipid antibodies (i.e., anticardiolipin or lupus anticoagulant) to a level that could trigger the clinical manifestations observed.

In view of the above, it seems that the rarity of post-influenza vaccination autoimmunity makes it difficult to establish a causal relation in most cases, even though a temporal association was documented. Furthermore, influenza vaccine, like most human vaccines, is capable of inducing immune responses similarly to influenza virus and includes also an adjuvant and other components that can increase its autoimmune pathogenicity. Thus, for the minority of individuals who are probably genetically susceptible [16], as well as for patients with active SLE disease, the influenza vaccine, among others, may trigger an overt autoimmune disease.

There is, last but not least, a paucity of clinical and epidemiological data on the potential of vaccines to induce autoimmune hazards. These adverse events, whether they appear days, weeks or months following vaccination, might be frequently overlooked. The awareness of physicians and caregivers to these associations and reports such as the one described in this issue by Vainer-Mossel et al. [5] might enable better assessment of post-vaccination complications as well as susceptibility and safety issues.

Correspondence:
Dr. Y. Shoenfeld
Head, Dept. of Medicine B, Sheba Medical Center, Tel Hashomer 52621, Israel
Phone: (972-3) 530-2652
Fax: (972-3) 535-2855.

References


**Capsule**

**Maternal alloantigens promote the development of tolerogenic fetal regulatory T cells in utero**

Fifty years ago,Billingham, Brent and Medawar first advanced the concept that “actively acquired immunologic tolerance” in the mouse occurs as a result of fetal exposure to foreign antigens. There have since been numerous reports suggesting that the transfer of foreign antigens (including proteins, parasites, and even cells) from the mother to the fetus is a common occurrence; however, the mechanism by which the fetal immune system recognizes and responds to such antigens is unclear. As the immune system develops, T cells are selected or regulated to become tolerant of self-antigens and reactive against foreign antigens. In mice, the induction of such tolerance is thought to be attributable to the deletion of self-reactive cells. Mold et al. show that the human fetal immune system takes advantage of an additional mechanism: the generation of regulatory T cells (Tregs) that suppress fetal immune responses. They found that substantial numbers of maternal cells cross the placenta to reside in fetal lymph nodes, inducing the development of CD4+CD25highFoxP3+ Tregs that suppress fetal antimaternal immunity and persist at least until early adulthood. These findings reveal a form of antigen-specific tolerance in humans, induced in utero and probably active in regulating immune responses after birth.

*Science* 2008; 322: 1562

Eitan Israeli

**Capsule**

**Mycobacterium tuberculosis** migrations and variations

Once it was thought that *Mycobacterium tuberculosis* was genetically uniform. However, global surveys of clinical samples have shown that like other human-specific pathogens, it has a marked biogeography. Hershberg et al. compared 90 genes in over 100 strains of the tuberculosis bacterium and established that the geographic variation has arisen as a consequence of human migrations over the millennia – first by land out of Africa 50,000 years ago and then by sea back to Africa over the past few centuries – and subsequent genetic drift rather than immune selection. In the apparent absence of purifying selection, many of the mutations are retained and result in non-synonymous changes in amino acids, which are likely to have functional effects. It is not clear how *M. tuberculosis* tolerates the potentially deleterious consequences of genetic drift, but this cryptic variation needs to be taken into account in vaccine and drug design.


Eitan Israeli