Influenza Vaccine and Autoimmunity

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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] rerely 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 casual relationship between the vaccine and this autoimmune neurological disease was noted in 1976 during an out-

SLE = systemic lupus erythematosus
APS = antiphospholipid syndrome
aCL = anticardiolipin

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-inflamatory 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.

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