

Adjuvants and Autoimmunity: Why Do We Develop Autoantibodies, Autoimmune Diseases and Lymphomas

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The word adjuvant comes from the Latin word *adjuvare* meaning “to help”. Adjuvants contain immunological characteristics, which enhance the immune system activity. They are normally incorporated into vaccines for more effective immunization, but they are also derived from many substances such as oils, minerals, bacteria and drugs. However, exposure to infectious agents or adjuvants can lead to the development of diverse autoimmune diseases in those who are genetically predisposed. The correlation between adjuvants (i.e., aluminum) and the onset or exacerbation of autoimmune diseases has been reported in case reports and series as well as in studies with animal models. Aluminum, which is found in many vaccines such as the hepatitis B virus (HBV) and human papillomavirus (HPV) vaccines, has been reported to induce autoimmune phenomena in those with a genetic tendency for autoimmunity, thus exacerbating rheumatic diseases and even the development of lymphomas. Silicone is another example of a material that possesses adjuvant activity. Silicone has been reported to induce diverse autoimmune conditions such as systemic sclerosis, as well as lymphoproliferative disorders such as the anaplastic large B-cell lymphoma. Physicians should be aware of the causal relationship that exists between adjuvant

materials and lymphomas, immunological reactions, and autoimmune diseases. Personalized medicine is warranted in the world of immunization to avoid unnecessary vaccinations or to follow-up on those at high risk for developing autoimmune diseases who were vaccinated.

The reason and mechanism behind the development of autoimmune diseases is very complex and multi-factorial, but they include a genetic tendency. Members within the same family can develop different autoimmune diseases, while others may remain unaffected [1]. Autoimmune diseases can arise from multiple causes and the interactions between these various factors contribute to the development of an autoimmune condition (i.e., the mosaic of autoimmunity). Genetic predisposition plays a pivotal role in all autoimmune diseases [2,3]. Indeed, those with such a proclivity have a very active and effective immune system. Although being immunocompetent and genetically susceptible to human leukocyte antigens (HLA)-DR4 and HLA-DRB1 means greater protection against infection, hyperactivity of the immune system may be associated with undesirable immune reactions and eventually autoimmune diseases.

There are specific genes associated with various autoimmune diseases. For example, more than 40 genes are implicated in the etiopathogenesis and development of systemic lupus erythematosus (SLE) [4]. However, the HLA system is the main player in determining the genetic predisposition for autoimmunity. In fact, the HLA-DRB1 haplotypes were found to

be involved in more than 30 diverse autoimmune diseases [5]. These specific haplotypes represent those who have a hyperactive immune system, which may confer an advantage to the evolution in terms of efficacy in confrontation with various infectious agents. Moreover, individuals with HLA-DRB1 produce more autoantibodies compared to normal controls.

In addition, females have a particularly effective immune system and therefore it is not surprising that 78% of autoimmune diseases are more common in women [1]. The lymphocytes of females contain receptors for estrogen that, once activated, lead to the secretion of B lymphocyte stimulator (BlyS), which stimulates the B cells and eventually produces autoantibodies. Environmental factors including drugs, vaccines and infectious agents contain substances with the characteristics and activity of adjuvants (immunostimulant effects). Adjuvants are normally used in vaccines to potentiate the reaction and produce a more effective immunization reaction. By stimulating the immune system and conferring protection against infection, vaccines may reduce the risk of developing autoimmune diseases. Conversely, studies about post-vaccination effects on the immune system report that vaccines may trigger the onset of autoimmune diseases [6]. As a result, the bi-directional relationship of vaccines and autoimmune diseases should be considered carefully when discussing the benefits and risks of vaccination in those genetically prone to developing autoimmune diseases.

ADJUVANTS AND AUTOIMMUNITY

An adjuvant is normally present in vaccines, but is also found in bacteria, drugs and other environmental agents [Figure 1]. Adjuvants stimulate the immune system, and therefore lead to more effective immune reactions [7]. Interestingly, by 1956, Noel Rose had already injected thyroglobulin (Tg) into animal models, which led to the production of Tg antibodies without thyroid disease. He succeeded in generating autoimmune thyroiditis only after adding an adjuvant to the Tg antigen. Aluminum is the main type of adjuvant used in human vaccines [8]. It can interact with dendritic cells, enhancing antigen presentation, stimulating toll-like receptors and complementing eosinophil activation, as well as promoting an influx of neutrophils and enhancing the secretion of pro-inflammatory cytokines and chemokines [8].

Despite the benefits of adjuvant use in vaccination, such additives can induce non-specific constitutional musculoskeletal or neurological clinical manifestations, and in certain cases can lead to the appearance or acceleration of an autoimmune disease in a patient with a genetic susceptibility [9].

During the building reconstruction that followed the 9/11 terrorist attacks in New York City, workers were exposed to aluminum in structures that remained intact after the disaster. Those who were involved in this work were reported to have an increased incidence of various autoimmune diseases including SLE, myositis, and Sjögren's syndrome [10].

In addition, several individual case reports have suggested a relationship between human papilloma virus (HPV)

vaccines containing aluminum adjuvant and the onset or exacerbation of autoimmune conditions [11]. Despite its adverse effects, aluminum is still widely used by most pharmaceutical companies due to its low price and efficacy in stimulating the immune system.

The induction of autoimmune diseases by adjuvants was also reported in animal models [8,12]. Agmon-Levin and colleagues [12] showed that mice inoculated with hepatitis B vaccine (HBV) had lower red blood cell counts, higher anti-double stranded DNA (anti-dsDNA) antibody levels, higher urine protein levels and more neurological disorders compared to mice inoculated with primary biliary cirrhosis (PBS) [12]. Another example for the induction of an autoimmune disease by vaccine in an animal model study was shown by a Japanese group, using the experimental autoimmune encephalitis (EAE) model [13]. The injection of HPV vaccine combined with pertussis toxin in EAE mice led to hypothalamic destruction with vascular cell apoptosis.

ADJUVANTS AND LYMPHOMAS

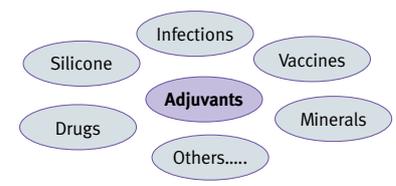
Lymphoma has been reported with higher prevalence among patients with autoimmune diseases [14]. The classic example of a disease exhibiting the association between autoimmunity and lymphoma is Sjögren's syndrome. The chronic stimulation of B cells in patients with this disease has been implicated as the causative mechanism in the development of lymphomas. The development of lymphomas due to the exposure to adjuvants comprises various steps, starting with lymphocytic infiltration, polyclonal B-cell activation and the production of pseudolymphoma production that eventually develops into a lymphoma, such as MALToma. In support of this claim, when aluminum was injected into the NZM-2758 mice strain, it induced the production of antinuclear antibody and Sjögren's syndrome-like disorders characterized by chronic salivary gland and periductal and peri-acinal lymphocytic infiltrates [15]. Another

correlation between adjuvants and lymphoma is represented by silicone breast implantations [16]. In women who already display a higher genetic risk for autoimmunity, silicone implantation might be a trigger for the development of autoimmune diseases such as systemic sclerosis. Silicone, as a material for implants, was selected because of its consistency and the belief that it is an inert substance that does not infiltrate the adjacent tissues. Today we know that silicone infiltrates the peri-mammillary tissues. This condition is known as "bleeding" of the silicone implants, and it can also be found in the axillar, and even inguinal, lymph nodes [18]. Interestingly, a tumor-denominated anaplastic large lymphoma, exclusively affects those with silicone implantation. Therefore, silicone has immunological effects that may cause a chronic activation of B cells and eventually lead to the development of lymphoproliferative disorders [17]. Furthermore, Neshet and co-authors [18] reported a case report of four women with ruptured silicone breast implants. The report describes the silicone infiltration into lymph nodes leading to silicone-containing granulomas.

CONCLUSIONS

In summary, adjuvants can be found in various materials, such as vaccines, bacteria, oil and other environmental factors. The interaction between the adjuvant material and genetic predisposition may lead to the development of autoimmune diseases as well as lymphoproliferative disorders [19]. The best example to simplify this complex link between adjuvants and autoimmunity is given by the recent description of ASIA syndrome by Shoenfeld et al. [20]. This syndrome is characterized by atypical manifestations of autoimmune diseases that affect individuals with genetic tendency for autoimmunity who have been exposed to various adjuvants. ASIA syndrome may be presented as well-defined autoimmune diseases or as non-specific autoimmune phenomena such as arthralgia, myalgia, and fatigue [21]. The onset of ASIA has

Figure 1. Various materials that contain substances with an adjuvant activity



been reportedly associated with almost all types of vaccines. Therefore, physicians should be aware of the presence of complications following vaccination or silicone implantation and apply screening strategies for autoimmune diseases and lymphoproliferative disorders to make early diagnoses and to treat them properly.

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Capsule

Randomized controlled trial of rituximab and cost-effectiveness analysis in treating fatigue and oral dryness in primary Sjögren's syndrome

To investigate whether rituximab, an anti-B cell therapy, improves symptoms of fatigue and oral dryness in patients with primary Sjögren's syndrome, Bowman and co-authors conducted a multi-center, randomized, double-blind, placebo-controlled, parallel-group trial that included health economic analysis. Anti-Ro-positive patients with primary Sjögren's syndrome, symptomatic fatigue, and oral dryness were recruited from 25 UK rheumatology clinics from August 2011 to January 2014. Patients were centrally randomized to receive either intravenous placebo (250 ml saline) or intravenous rituximab (1,000 mg in 250 ml saline) in two courses at weeks 0, 2, 24, and 26, with pre- and post-infusion medication, including corticosteroids. The primary endpoint was the proportion of patients achieving a 30% reduction in either fatigue or oral dryness at 48 weeks, as measured by visual analog scale. Other outcome measures included salivary and lacrimal flow rates, quality of life, scores on the European League Against Rheumatism (EULAR) Sjögren's Syndrome Patient Reported Index and EULAR Sjögren's Syndrome Disease Activity Index, symptoms of

ocular and overall dryness, pain, globally assessed disease activity, and cost-effectiveness. All 133 patients who were randomized to receive placebo (n=66) or rituximab (n=67) were included in the primary analysis. Among patients with complete data, 21 of 56 placebo-treated patients and 24 of 61 rituximab-treated patients achieved the primary endpoint. After multiple imputations of missing outcomes, response rates in the placebo and rituximab groups were 36.8% and 39.8%, respectively (adjusted odds ratio 1.13, 95% confidence interval 0.50–2.55). There were no significant improvements in any outcome measure except for unstimulated salivary flow. The mean ± standard deviation costs per patient for rituximab and placebo were £10,752 ± 264.75 and £2,672 ± 241.71, respectively. There were slightly more adverse events reported in total for rituximab, but there was no difference in serious adverse events (10 in each group). The results of this study indicate that rituximab is neither clinically effective nor cost-effective in this patient population.

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