

Vaccines and Autoimmune Diseases of the Adult

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Abstract: Infectious agents contribute to the environmental factors involved in the development of autoimmune diseases possibly through molecular mimicry mechanisms. Hence, it is feasible that vaccinations may also contribute to the mosaic of autoimmunity. Evidence for the association of vaccinations and the development of these diseases is presented in this review. Infrequently reported post-vaccination autoimmune diseases include systemic lupus erythematosus, rheumatoid arthritis, inflammatory myopathies, multiple sclerosis, Guillain-Barré syndrome, and vasculitis. In addition, we will discuss macrophagic myofasciitis, aluminum containing vaccines, and the recent evidence for autoimmunity following human papilloma virus vaccine.

Introduction

Systemic and organ derived autoimmune diseases are known to develop following infectious triggers. Recently we have suggested that certain autoimmune diseases like [systemic lupus erythematosus \(SLE\)](#) may result due to specific viral agents. Furthermore, the spectrum of disease may be influenced by a certain microbial agent in the genetically predisposed individual (Zandman-Goddard et al., 2009).

Vaccines are a prototypic source for natural immune stimulation, but may be involved in pathogenic disease in the setting of aberrant immune system function. Possibly, the burden on the immune system resulting from simultaneous multiple vaccines and even the different types of vaccines may also be an overwhelming challenge in the autoimmune prone individual (Shoenfeld et al., 2008). In this review, we discuss the evidence for the development of autoimmune diseases following infections.

While vaccinations are generally safe, warranted and have virtually eradicated endemic diseases and probably lessened morbidity and mortality, a question arises regarding the evaluation of possible autoimmune phenomena in vaccinated individuals.

Reported post-[vaccination](#) autoimmune diseases in the adult include SLE, [rheumatoid arthritis](#) (RA), [inflammatory myopathies](#), [multiple sclerosis](#) (MS), Guillain-Barré syndrome (GBS), and [vasculitis](#). Evidence for the association of vaccinations and the development of these diseases is presented in this review. In addition, we will discuss [macrophagic myofasciitis](#), post aluminum containing vaccines and the recent support for [autoimmunity](#) following human papilloma virus vaccine.

The Role of Infections in the Induction of Autoimmune Diseases

Infections, including viruses, bacteria, parasites and fungi, have pivotal roles as environmental factors contributing to the mosaic of autoimmune diseases (Shoenfeld et al., 2008).

Evidence exists for the association of streptococcus pyogenes infection with the development of rheumatic fever (Cunningham et al., 1988), *Trypanosoma cruzi* parasitic infection and Chagas disease cardiomyopathy (Cunha-Neto et al., 1995), the spirochete *Borrelia burgdorferii* and Lyme disease (Chen et al., 1999), *Campylobacter jejuni* infection and Guillain-Barré syndrome (Vucic et al., 2009; Khamaisi et al., 2004; Yuki, 2007), viral infections and [diabetes](#) mellitus I (Goldberg et al., 2009), *Chlamydia pneumoniae* and [Epstein-Barr virus](#) (EBV) and multiple sclerosis (Ercolini et al., 2009; Bagert, 2009), and EBV infection and SLE (Zandman-Goddard et al., 2009; Pender, 2003). Our group recently screened more than 1,300 patients with different autoimmune diseases and found a significant association of [hepatitis C virus](#) with other diseases including autoimmune thyroiditis, Crohn's disease, pemphigus vulgaris, antiphospholipid syndrome, and vasculitides. In addition, in this study, EBV was found to be linked to SLE, RA, pemphigus vulgaris, giant cell arteritis, Wegener's granulomatosis, polyarteritis nodosa, MS, Sjogren's syndrome, and polymyositis (Kivity et al., 2009).

The Role of Vaccines in the Induction of Autoimmune Diseases

SLE

SLE patients show decreased immune responsiveness and are vulnerable for [infectious diseases](#), due to the underlying disease and the frequent use of immunosuppressive drugs (Zandman-Goddard et al., 2005).

In studies of more than 10 patients, the reported manifestations following [hepatitis B](#) vaccination were arthritis, thrombocytopenia, demyelinating encephalitis, and demyelinating [neuropathy](#). A case-control study of 265 newly diagnosed lupus patients did not show that [HBV](#) vaccine was a risk factor for developing SLE [odds ratio (OR)-1.4] (Schattner, 2005). In a current study, 10 lupus patients were diagnosed within several days and up to one year following hepatitis B vaccination (Agmon-Levin et al., 2009). Previously, 11 cases were reported in the literature regarding the onset or exacerbation of SLE post hepatitis B vaccination (Schattner, 2005).

In concordance, a latency period of less than one week and up to 2 years between vaccination and SLE onset was reported. The classical period between vaccination and autoimmunity was considered to be several weeks, similarly to the time frame suggested in the past for post-infectious autoimmunity phenomena. Interestingly, in this case series, 70% of patients continued their [immunization](#) protocol although adverse events were documented. Similarly, in previously reported cases, the affected subjects continued to be vaccinated and aggravation of their condition by additional doses had been documented (Agmon-Levin et al., 2009). Overall, SLE patients presented post hepatitis B vaccination with mild to moderate disease and without life threatening organ involvement.

A summary of the serious autoimmune adverse events following vaccination with hepatitis B vaccination reported to the vaccine adverse events reporting system (VAERS) include in descending order by odds ratio: RA (OR-18), optic neuritis (OR-14), SLE (OR-9.1), alopecia (OR-7.2), MS (OR-5.2), and vasculitis

(OR-2.6). Many of the adverse events associated with hepatitis B vaccination were extra-hepatic and are manifestations of infection with HBV. In addition to the potential epitopes in the [HBsAg](#) (HBV surface antigen) vaccine, adjuvants containing aluminum and mercury may provide potential antigenic stimulation (Geier et al., 2005).

Routine [influenza](#) vaccination of SLE patients seems indicated although the activation of an autoimmune response is feasible. Of 10 studies on 265 SLE patients that received [influenza vaccine](#) (with a follow-up period of 4-24 weeks) only 6 were reported to develop a flare, of those two patients had renal involvement (Conti et al., 2008; Del Porto et al., 2008; Holvast et al., 2007; Abu-Shakra et al., 2007). It is not clear that the composition of the modern vaccines is identical to those of over 30 years ago where most of the studies were performed.

In SLE, the immune response to influenza vaccination led to a blunted humoral response (Holvast et al., 2007). Generally, in the lupus patient in remission, flares are infrequent and influenza vaccine can be administered without harm. Why a few lupus patients had a flare following influenza immunization as evaluated utilizing the systemic lupus erythematosus disease activity index (SLEDAI) score is yet to be established (Abu-Shakra et al., 2007).

In a small observational study on 24 lupus patients, the 23 serotype pneumococcal vaccine did not confer disease activity (Elkayam et al., 2005).

Multiple sclerosis

Neurological manifestations are common following vaccinations (Huynh et al., 2008). In a case-control epidemiological study for serious adverse events reported in the hepatitis B vaccination exposed group compared to those that received tetanus vaccine, MS was prominent with an odds ratio of 5.2 ($P < 0.0003$). Optic neuritis was also very commonly encountered (OR-14, $p < 0.0002$) (Geier et al., 2005).

Guillain-Barré syndrome

In GBS, activated macrophages invade intact myelin sheaths resulting in myelin damage and demyelination (Vucic et al., 2009).

Vaccines reported as associated with GBS are diverse (Schonberger et al., 1979; Hemachudha et al., 1988; Khamaisi et al., 2004; CDC, 2006; Slade et al., 2009; Haber et al., 2009). The evidence of casual relationship with GBS is strongest with the swine [flu \(H1N1\)](#) vaccine that was used in 1976-7. An increased relative risk [relative risk (RR)-4-8] to develop GBS 6-8 weeks after the injection was encountered in the vaccinated group compared to the non vaccinated group. The risk for GBS was slightly less than 1 excess case of GBS per 100,000 vaccinated individuals, and hence the vaccine program was suspended (Schonberger et al., 1979). Further studies substantiated the association between the H1N1 vaccine and an increased relative risk (RR-7/1) for GBS 6 weeks after the vaccine (Safraneck et al., 1991). The pathophysiology is unclear but may be related to vaccine induced anti-ganglioside antibodies (GM1) (Nachamkin et al., 2008).

Studies of influenza vaccines in the following years were not associated with a substantial increase in the rate of GBS (Lasky et al., 1998). Immunizing patients with a history of GBS requires caution.

An increased risk for GBS was found in Semple and SMB rabies vaccines. The vaccine most probably included brain protein that could cause cross reactive antibodies to the neural tissue and were discontinued. The current rabies vaccines are derived from chick embryo cells and are not associated with an increased rate of GBS (Hemachudha et al., 1988).

The vaccine against *Neisseria meningitides* is for use among individuals aged 11-55 years old. The VAERS published a warning of a possible association between the Meningococcal Polisaccharide Diphtheria Toxoid Conjugated Vaccine (MCV4) and GBS, because of 5 cases of GBS following the MCV4 vaccine, and later 12 additional cases were reported (CDC, 2005). Based on reports, statistical analysis did not show any significant increase in the rate of GBS occurring 6 weeks after the MCV4 vaccine compared to non-vaccinated population. However, it is recommended that individuals with a history of GBS should not be vaccinated with MCV4 unless they are in a high risk for meningococcal infection. In a mass meningococcal C conjugate vaccine (CMCV not MCV4) campaign in Quebec, Canada in 2001, 2 cases of GBS 8 weeks after the vaccine were identified among 1.5 million administered vaccinations, a rate expected in the healthy normal population (De Wals et al., 2008).

The FDA licensed the quadrivalent human papilloamavirus recombinant vaccine (qHPV) in the United States in June 2006 for use in females 9-26 years old. In a review of the adverse effects reported over two years to the VAERS (Slade et al., 2009), 12 of 42 cases reported as GBS were confirmed, 11 of them in the age 13-30 years old. Only eight of the confirmed cases were in the range of 4-42 days post vaccination. The relative risk in 9-26 year old females vaccinated with qHPV vaccine for GBS was low (Callreus et al., 2009).

Vaccine induced myopathies

The reports on vaccine induced inflammatory myopathies are sporadic and include cases of following immunization with HBV, bacillus Calmette-Guérin, tetanus, influenza, [smallpox](#), polio, diphtheria, or combinations with diphtheria (Orbach et al., 2009). There is no statistically significant increase in the incidence of polymyositis or dermatomyositis after any mass vaccination. Among 289 patients with inflammatory myopathies followed in the Mayo Clinic, no recent immunization was recorded (Winkelman, 1968; Winkelmann, 1982).

Macrophagic myofasciitis

Macrophagic myofasciitis is a reaction to intramuscular injections of vaccines containing aluminum hydroxide as an adjuvant and affects mainly adults. The symptoms are usually myalgia, arthralgia, asthenia and, less frequently, muscle weakness and fever, in the presence of elevated creatine kinase and erythrocyte sedimentation rates. The electromyogram has a unique pathologic pattern characterized mainly by focal infiltration of the epimysium, perimysium, and perifascicular endomysium by sheets of large, non-epithelioid macrophages, which show fine granular staining for periodic acid-Schiff (PAS) stain that appear as small, osmiophilic, spiky structures on [electron microscopy](#), representing the aluminum hydroxide crystals (Gherardi et al., 2001). Immunizations containing aluminum may trigger Macrophagic myofasciitis in the context of an [HLA-DRB1*01](#) genetic background (Guis et al., 2002). Frequently, patients improve with steroid therapy.

Vasculitis

Numerous case reports reported a possible association between polyarteritis nodosa (PAN) and hepatitis B vaccination. Overall, 25 cases of PAN were submitted to VAERS over an 11 year period until 2001. Among them, only 10 individuals were diagnosed as definite or possible PAN and are discussed here. The median age of patients was 45 years old and 5 patients were hospitalized. A modal peak of 2 weeks and median of 2.8 weeks post-vaccination was noted. All cases received at least 2 doses of vaccine prior to symptom onset. Hepatitis B surface antigenemia frequently follows hepatitis B vaccination and is detected many days after the 20 microgram vaccine. This could explain related immune-complex disease. Recently, there were less than 20 reports on the development of vasculitis following influenza vaccination. Small, medium, and large vessels were involved (Begier et al., 2004). All in all, this would be considered a rare event.

Rheumatoid arthritis

A total of 48 out of 898 (5.3%) of patients with early inflammatory polyarthritis reported an immunization in the 5 weeks prior to symptom onset. There were no important clinical or demographic differences between the 48 immunized patients and 185 consecutive patients who did not report prior immunization. The frequencies of HLA DRB1 *01 and *04 and the shared epitope in 33 of the immunized patients were no different in the non-immunized patients compared to healthy controls. Possibly, in a small number of susceptible individuals, immunization may act as a trigger for RA (Harrison et al., 1997).

Seropositive [HLA-DR4](#)-positive RA is reported in a few case reports after hepatitis B vaccination. In a series of 11 patients who developed RA after hepatitis B vaccination, all individuals were healthy prior to vaccination and they developed persistent polyarthritis fulfilling the present American College of [Rheumatology](#) criteria for RA (Pope et al., 1998). Five subjects expressed HLA-DR4, and HLA class II genes with the RA shared motif were identified in nine of 11 patients. In a case-control epidemiological study, adults receiving hepatitis B vaccination had an odds ratio of 18 to develop RA ($P < 0.0001$) (Geier et al., 2005). However, the available data suggests a benefit of the vaccine that outweighs the risk (Sibilia et al., 2002).

RA patients have almost a doubled risk level of developing an infection in comparison with age- and sex-matched subjects. In two randomized studies on RA patients, a good safety profile for the influenza vaccine without an increased rate of exacerbation was shown (Conti et al., 2008). Ninety nine [adalimumab](#) treated patients had a less significant immune response than 99 placebo treated RA, but the difference was not statistically relevant (Kaine et al., 2007). Infliximab and etanercept did not influence the immunogenicity of influenza vaccine (Kubota et al., 2007). The effect of [rituximab](#) on the efficacy and immunogenicity of influenza vaccine was studied in 14 RA patients. During the 4-week follow-up after vaccination, there was no difference in disease activity in both groups of patients. In the [rituximab](#) treated patients, the percentage of responders was low for all three antigens tested, achieving statistical significance for the California antigen (Oren et al., 2008).

The safety profile of pneumococcal vaccine was good without exacerbations of RA (Elkayam et al., 2002). In 5 studies on the immunogenicity of the pneumococcal vaccine in RA patients, elevated titers of antibodies occurred but the response was partial. In 11 RA patients treated with [TNF- \$\alpha\$](#) blockers, the titer of the antibodies increased to a lower level compared to other disease modifying anti-rheumatic drugs ([DMARDs](#)) treated RA patients. In another study, [methotrexate](#) treated patients had an inferior increase in antibodies to the 23F and B6 serotypes when compared to patients treated by [TNF- \$\alpha\$](#) blockers and healthy controls. In the Aspire trial, 70 RA patients with early disease were immunized by pneumococcal vaccine 34 weeks after initiating therapy. The percentage of patients with antibody response was similar in the three groups (infliximab at 2 different doses with methotrexate or methotrexate alone) (20-25% response). All treatment groups had a lower response to vaccine than would be expected in the normal population. Interestingly, the addition of infliximab to methotrexate therapy did not impair the immune response (Visvanathan et al., 2007).

Hepatitis B vaccination was safe in 22 RA patients compared to controls without any evidence of exacerbation of the disease and was effective in 68% of patients (Elkayam et al., 2002).

[HPV vaccine](#) and autoimmune manifestations

The recently released vaccine for [human papillomavirus \(HPV\)](#) offers an opportunity to assess the development of autoimmune phenomena in a high risk population of young women. Hence, we chose to investigate and report separately on this vaccine.

Recently developed vaccines against human papillomavirus (HPV) and [hepatitis B virus \(HBV\)](#) contain a novel Adjuvant System, AS04, which is composed of 3-O-desacyl-4' monophosphoryl lipid A and

aluminum salts. All randomized, controlled trials of [HPV-16/18](#), [herpes simplex virus \(HSV\)](#), and HBV vaccines were analyzed in an integrated analysis of individual data (N = 68,512). A separate analysis of the HPV-16/18 vaccine trials alone was also undertaken (N = 39,160). The reported rates of overall autoimmune events were around 0.5% and did not differ between the AS04 and control groups. The relative risk (AS04/control) of experiencing any autoimmune event was 0.98 (95% confidence intervals 0.80, 1.21) in the integrated analysis and 0.92 (0.70, 1.22) in the HPV-16/18 vaccine analysis. This integrated analysis of over 68,000 participants who received AS04 adjuvant vaccines or controls demonstrated a low rate of autoimmune disorders, without evidence of an increase in relative risk associated with AS04 adjuvanted vaccines (Verstraeten et al., 2008).

In the Danish Civil Registration system, among approximately half a million adolescent girls, 414 autoimmune disorders were listed. The 5 most common autoimmune diseases occurring within 6 weeks of vaccination among 100,000 girls were: type I diabetes, juvenile arthritis, Crohn's disease, Henoch-Schonlein disease, and [ulcerative colitis](#) (Sutton et al., 2009). However, over a 10 year period, the common autoimmune diseases, from the most to the least common, were: type I diabetes, juvenile arthritis, Crohn's disease, ulcerative colitis, Basedow's disease, Henoch-Schonlein purpura, [psoriasis](#), and SLE (Verstraeten et al., 2008).

Adverse events of potential autoimmune etiology for HPV 16/18, HBV, and genital HSV vaccine trials (n = 42) were evaluated in an integrated analysis of 68,512 individuals. Common to these 3 vaccines is their adjuvant, AS04. A separate analysis of HPV 16/18 vaccine trials was performed in an integrated analysis of 39,160 individuals. The analysis included all completed or ongoing controlled randomized studies of the 3 vaccines conducted by GlaxoSmithKline Biologicals or collaborators. No independent sources on this subject were retrieved in a literature search. The control group received vaccines that were AS04 free, non-adjuvanted, or adjuvanted with aluminum or aluminum hydroxide. To be included in the analysis, each individual received at least one dose of vaccine. The mean follow-up period was 1.8 years. These studies were not specifically set up to evaluate the development of autoimmune phenomena. A total of 362 participants reported at least one autoimmune event with an event rate of 0.52% in the vaccinated group which did not differ from the control group (0.54%). Hypothyroidism was the most common individual event, followed by unclassified musculoskeletal and neuroinflammatory disorders.

The overall relative risk for developing an [autoimmune disease](#) was 0.98, hence no direct statistically significant difference between the groups was encountered. However, when looking at each disease individually, the highest relative risk for an individual event was idiopathic thrombocytopenic purpura (RR-3.74), followed by SLE (RR-3.00). For organ specific disease, thyroid involvement was most commonly detected. For analysis of the entire database which included data for HBV and HSV vaccine as well, the highest relative risk for an individual event was for SLE (RR-2.39) (Verstraeten et al., 2008).

Discussion

Autoimmune diseases that are known to be infection induced and can be prevented by proper therapy in most cases include rheumatic fever and Lyme disease. A most probable causality occurred between exposure to swine [flu vaccine](#) and the development of GBS. In addition, MMF occurred following exposure to aluminum containing adjuvant. Vaccines, like infections, activate immune mediated mechanisms to induce a protective effect. Hence, a complex vaccine may theoretically be more immunogenic than a simple vaccine. Vaccines harbor added complex agents, for example, adjuvants including aluminum, which may induce autoimmune disease. Preservatives are more often found in viral vaccines compared to bacterial vaccines suggesting that the preservatives may be the inciting culprits (Israeli et al., 2009).

Given the background incidence of autoimmune disorders in some of the groups targeted for immunization with these vaccines, it is likely that autoimmune events will be reported in temporal association with vaccination, even in the absence of a causal relationship (**Table 1**).

Table 1. Association of Vaccines with Autoimmune Disease		
Type of vaccine	Autoimmune disease	Reference
Influenza	GBS	Schonberger et al., 1979
Meningococcal (MCV4)	GBS	CDC, 2006
HBV	MS, SLE, RA	Geier et al., 2005
HPV	IDDM , IBD, vasculitis, SLE	Verstraeten et al., 2008; Sutton et al., 2009
MMR	ITP-like	Wraith et al., 2003
HAV, HBV, TT	Macrophagic myofasciitis	Gherardi et al., 2001
GBS, Guillain-Barré syndrome; SLE, systemic lupus erythematosus; MS, multiple sclerosis; ITP, idiopathic thrombocytopenic purpura; IDDM, insulin dependent diabetes mellitus; IBD, inflammatory bowel disease ; HAV, hepatitis A virus; TT, tetanus toxoid.		

A comprehensive strategy is required to develop a new vaccine that will not induce autoimmune manifestations as previously proposed. Looking in the future, experimental investigation may discover autoimmune phenomena in spontaneous and naïve disease models.

Perhaps, the assessment of [autoantibody](#) and HLA status prior to immunization will serve as a marker for individuals at risk. More research is required to identify those individuals who may develop autoimmune diseases following immunizations. It is not clear if genomics or [proteomics](#) will reveal the individuals with an increased risk to develop autoimmune phenomena.

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