Vaccinations and Autoimmune Diseases

Subjects: Infectious Diseases

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Vaccines represent one of the most effective measures of public health medicine, saving countless lives and preventing lifelong disabilities. Among the adverse reactions to vaccines, one of the most feared is the triggering of autoimmune diseases, which are a heterogeneous group of disorders characterized by dysregulation of the immune system. Currently, no mechanisms have been demonstrated that could explain the correlation between vaccination and the development of autoimmune diseases. Furthermore, epidemiological studies do not support the hypothesis that vaccines cause systemic autoimmune diseases. The only confirmed associations, although very rare, are those between the flu vaccine and Guillain-Barré syndrome, especially with old vaccine preparations, and measles-mumps-rubella (MMR) vaccine and thrombocytopenia.

Keywords: vaccines ; autoimmunity ; autoimmune diseases ; Guillain-Barré syndrome ; thrombocytopenia ; SARS-CoV2 vaccines ; vaccine-induced immune thrombotic thrombocytopenia

1. Introduction

Immunization is one of the most effective measures of public health medicine, saving countless lives and preventing lifelong disabilities. Vaccines are extremely effective, highly safe, and are mostly affordable; therefore, they have allowed not only a reduction in the incidence of infections, but also a reduction in the mortality and morbidity related to them[1].

However, no vaccine is completely free of risk and adverse reactions will occasionally occur following vaccination[2]. Reported adverse event following immunization (AEFI) may be proven adverse reactions, caused by the vaccine or the immunization process, or events that temporally occurred after immunization but are not caused by it. Causality assessment is meant to assist in determining the level of certainty of an association between the immunization and an AEFI, which may be classified as consistent, inconsistent, or indeterminate[3].

Adverse reactions caused by vaccines are much lower in frequency and severity than those caused by spontaneous infection. The majority of adverse reactions are mild, such as injection site pain or fever, and only a small number of cases may be very serious or require medical attention[4][5]. Despite significant benefits of vaccination, misconceptions about vaccine safety still affect public confidence and hesitancy can reduce adherence to immunization programs[6]. Among the adverse reactions to vaccines, one of the most feared is the triggering of autoimmune diseases[7].

Except for the rare associations between flu vaccine and Guillain-Barré syndrome and between measles-mumps-rubella vaccine (MMR) and thrombocytopenia, the role of vaccines in the development of autoimmune diseases has not been established[8][9]. Many isolated cases or case series of arthritis, vasculitis and central or peripheral nervous system symptoms in temporal relationship with vaccination are reported as AEFI in the scientific literature; despite this, currently no mechanisms have been demonstrated that can explain the correlation between vaccination and the development of chronic autoimmune diseases. Furthermore, epidemiological studies do not support the hypothesis that vaccines cause systemic autoimmune diseases[7][10].

2. Live Attenuated Vaccines: Measles-Mumps-Rubella and Varicella-Zoster

Vaccine-preventable viral diseases can cause serious complications and rarely death.

The availability of live attenuated measles, mumps and rubella vaccines has almost completely eliminated serious neurologic complications of measles and dramatically reduced cases of congenital rubella[11][12][13]. These vaccines are currently administered in trivalent MMR vaccine. Varicella vaccine can be single antigen or combined with measles, mumps, rubella and varicella (MMRV). The most significant adverse event reported following MMR vaccination is thrombocytopenic purpura, which is consistent with the immune-mediated manifestations documented after wild virus infections, although much rarer. After MMR vaccination, there have also been very rare cases of anterior uveitis[14][15],

retinopathy[16], vasculitis, and myositis[10][17]. Several AEFI have been reported to the US Vaccine Adverse Events Reporting System (VAERS) after varicella vaccination. However, this passive surveillance system records data of suspected adverse reactions but does not assess causal relationship[10][18][19].

Idiopathic thrombocytopenic purpura (ITP) has been confirmed as a rare adverse reaction after MMR vaccination[20][21]. The median time to onset of thrombocytopenia is 12–25 days after immunization, but the range is 1–83 days[2]. However, the risk of ITP after vaccination is smaller than after natural infection with these viruses[22][23].

Episodes of transient arthralgia (in 25% of cases) and acute arthritis following MMR vaccination are reported. These joint manifestations are due to the rubella virus component present in the MMR vaccine[2]. Acute arthritis onset usually occurs within six weeks of immunization; after this period it is unlikely that arthritis is related to the vaccine[24].

An increase in cases of aseptic meningitis has been reported since 1989 with varying frequencies in different countries. This increase was due to the presence of UrabeAM9 mump strain. Urabe-containing vaccines were withdrawn from the market after this finding[25]. Currently there is no evidence of an association between MMR immunization and aseptic meningitis, encephalitis and encephalopathy. Furthermore, there is also no causal correlation between MMR vaccine and autistic spectrum disorders[22].

At present, it has not been possible to demonstrate a statistically significant association between MMR vaccination and Guillain-Barré syndrome. Moreover, there is no evidence to support an association between MMR immunization and type 1 diabetes mellitus (DM-1), and multiple sclerosis according to a recent meta-analysis[22].

Zoster vaccine is a live attenuated vaccine recommended for older adults to reduce the incidence of herpes zoster and its complication of postherpetic neuralgia. A case-control study of reported events to the VAERS showed no significantly increased risk of severe autoimmune events after vaccination, except for arthritis and alopecia (respectively 2.2 and 2.7 time the odds compared to unexposed subjects)[26].

3. Recombinant DNA Vaccine: Hepatitis B

The frequency of autoimmune manifestations reported after administration of the HBV vaccine, based on recombinant DNA technology to express HBsAg, is extremely low compared to the tens of millions of vaccinations performed[10]. Cases of arthritis, rheumatoid arthritis (RA)[27][28], thrombocytopenia[29], vasculitis[30], demyelinating encephalitis[31], and other neurological manifestations have been reported[32][33].

There is currently insufficient evidence to establish a causal link between the HBV vaccine and encephalitis, acute disseminated encephalomyelitis (ADEM), transverse myelitis, optic neuritis, multiple sclerosis, Guillain-Barré syndrome, brachial neuritis, erythema nodosum, reactive arthritis, psoriatic arthritis, rheumatoid arthritis, juvenile idiopathic arthritis, DM-1, fibromyalgia, onset or exacerbation of Systemic Lupus Erythematosus (SLE) and vasculitis[34].

Independent scientific institutions, such as the WHO and the WHO's GACVS and the US Institute of Medicine (IOM), have not found a link between HBV vaccination and autoimmune manifestations[35][36].

4. Inactivated Vaccines: Influenza

Influenza is an acute viral respiratory disease that can cause hundreds of thousands of hospitalizations and thousands of deaths during annual winter epidemics[37].

Influenza virus infection can sometimes be implicated in autoimmune complications, such as multiple sclerosis, Guillain-Barré syndrome, epilepsy, DM-1, Schönlein-Henoch syndrome, antiphospholipid syndrome, acute encephalomyelitis, thrombocytopenia and myocarditis[38][39]. After influenza vaccination, cases of vasculitis and rare cases of neurological diseases (e.g., Guillain-Barré syndrome), Schönlein-Henoch syndrome, rheumatoid vasculitis and microscopic polyangiitis have been described[39].

Regarding influenza vaccination and Guillain-Barré syndrome, a sudden increase in cases recorded after the 1976 mass vaccination program in the US was related to the swine influenza A/New Jersey/76 vaccine; therefore, the program was suspended that same year. In the following years, vaccines were prepared with other influenza viruses, resulting in no significant subsequent increase in cases of Guillain-Barrè syndrome[40][41]. The association between the influenza vaccine and Guillain-Barré syndrome was closely monitored, noting a slightly increased risk in some seasons but not in others. In any case, the attributable risk of Guillain-Barré syndrome after influenza vaccination in adults is estimated to be 1–3 in

1,000,000, confirming that it is a very rare event[9]. However, it is important to consider that influenza virus infection carries a greater risk of developing Guillain-Barré syndrome than influenza vaccination. Hence, during an entire flu season, influenza vaccination reduces the risk of developing Guillain-Barré syndrome[42].

5. Vaccines against Invasive Infections by Encapsulated Bacteria: Meningococcal, Pneumococcal, Haemophilus Influenzae Type b Vaccines

Meningitis is a public health problem in most countries, with a morbidity of 1–5 per 100,000 in developed countries and 10–25 per 100,000 in developing countries. The mortality linked to meningococcal meningitis is 5–10%, but reaches 15–20% for fulminant septicemia[2].

There are two types of meningococcal vaccines: meningococcal conjugate (MenC and tetravalent MenACWY135) and serogroup B meningococcal (or MenB) vaccines. During a mass immunization campaign against meningococcus C with conjugated and unconjugated vaccines conducted in France in 2002, the most frequent adverse events were local, neurological and gastrointestinal reactions, mostly transient and not serious. Only 13 serious adverse events were reported, including serum sickness, arthritis, purpura, facial paralysis, multiple sclerosis and meningism. No significant differences were found in the rates of adverse event reports between both vaccines[43]. Immunization with the meningococcal conjugated tetravalent vaccine has not been associated with particular safety concerns or with autoimmune manifestations[44].

The introduction of the pneumococcal conjugate vaccine has significantly reduced the incidence of pneumococcal infections, including invasive pneumococcal diseases[2].

The conjugate pneumococcal vaccine showed a high level of safety. Rare immune-mediated adverse events (e.g., vasculitis, thrombocytopenia, arthritis or arthralgias etc.) temporally correlated with the administration of the vaccine have been reported to passive pharmacovigilance systems but the causal association remains only hypothetical[45].

Haemophilus influenzae type (Hib) is a common cause of bacterial meningitis, pneumonia, and septicemia in children, but can also cause cellulitis (often facial), septic arthritis, and osteomyelitis[2].

To date, no significant associations have been reported between Hib and the onset of autoimmune manifestations. A hypothetical increased risk of developing DM-1 in childhood following vaccination[46] was subsequently disproved by further studies[47][48].

6. Human Papilloma Virus Vaccines

Human Papilloma Virus (HPV) infection represents the most common sexually transmitted viral infection of the genital tract and is a leading cause of cervical cancer. The morbidity of cervical cancer is about 0.5 million cases per year, while mortality is about 0.25 million cases per year[2].

HPV vaccines are an important means of reducing the incidence of cervical cancer. These vaccines contain non-infectious virus-like particles obtained by recombinant DNA technology[49].

Despite the theoretical hypothesis that HPV vaccination may contribute to the onset of autoimmune diseases, recent large-scale studies provide reassuring results. A large population-based cohort study conducted in Denmark and Sweden analyzed more than 696,000 doses of quadrivalent HPV vaccine among females and found no consistent evidence supporting causal associations with several autoimmune and neurologic conditions[50]. These data were also confirmed by a French large case-control study[51]. An analysis of national data from Sweden and Denmark found no increased risk of multiple sclerosis or other demyelinating diseases following HPV vaccination[52]. A meta-analysis that included 20 studies (12 cohort studies, 6 case-control studies, and 2 randomized controlled trials) showed that HPV vaccination was not associated with an increased risk of autoimmune diseases[53].

7. SARS-CoV2 Vaccines

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) is an RNA-virus that causes Coronavirus disease 2019 (COVID-19), responsible for the 2020 worldwide pandemic[54]. The immune system appears to play a dual role in SARS-CoV2 infection, both for its activity to control the infection, and its dysregulated response involved in the acute progression of the disease. Therefore it has been hypothesized that this immune dysregulation could induce the loss of tolerance and trigger chronic inflammation[55]. In fact, many cases of autoantibody production, such as anti-nuclear antibodies, have been reported during COVID-19 infection[56]. Various case reports of autoimmune diseases secondary to SARS-CoV2

infection are described in the literature[57], i.e., immune thrombocytopenic purpura[58][59], autoimmune hemolytic anemia[60][61], Guillain-Barré syndrome[62][63][64], Miller Fisher syndrome[65], antiphospholipid syndrome[66][67] and Kawasaki-like disease[68][69].

The types of vaccines currently on the market are mRNA vaccines and virus-vectored vaccines[70]. Studies currently confirm the overall safety and efficacy of available vaccines[71][72][73][74]. However, rare cases of vaccine-induced immune thrombotic thrombocytopenia (VITT) have been recently reported 5 to 16 days after administration of adenovirus viral-vector vaccines. Most patients were women with a mean age of 36 years (range 22 to 49 years old). VITT consists of severe thrombocytopenia associated with thrombotic phenomena, often in atypical sites, such as cerebral venous thrombosis, splanchnic veins thrombosis, pulmonary embolism, and other types of thrombi. Some patients had more than one thrombotic event at the same time and others had disseminated intravascular coagulation (DIC). In a majority of the patients the outcome was fatal[75][76][77]. In patients with VITT, high levels of antibodies to platelet factor 4 (PF4)–polyanion complexes were identified by enzyme-linked immunosorbent assay (ELISA). In contrast to heparin-induced thrombocytopenia (HIT), binding of antibody to PF4 occurred in the absence of heparin[78].

The risk of venous thromboembolism associated with the vaccines appears to be not higher than the background risk in the general population. These data are important for evaluating the favorable risk-benefit ratio for SARS-CoV-2 vaccines. It is essential that close safety monitoring of these new vaccines continues[79].

As for other autoimmune manifestations, case reports of Guillain-Barré syndrome after administration of anti-SARS-CoV2 vaccine have been described[80][81]. However, further studies are needed to evaluate the immune-mediated effects of these new vaccines.

8. Vaccinations in Patients with Rheumatic Autoimmune Diseases

Patients with autoimmune inflammatory rheumatic diseases are at increased risk of vaccine-preventable infections, such as influenza, pneumococcal, herpes zoster and HPV infections. For this reason the prevention of these infections is essential in these type of patients[82]. The European League Against Rheumatism (EULAR) recommendations regarding vaccinations in patients with rheumatological diseases have recently been published. Generally, it is preferable to vaccinate the patient during the quiescent phase of the rheumatological disease and, if possible, to plan the vaccination before starting immunosuppression, in particular B cell depleting therapy. Non-live vaccines can also be administered to patients during treatment with systemic glucocorticoids and disease-modifying antirheumatic drugs (DMARDs), while administration of live attenuated vaccines should be considered with caution. In clinical practice, influenza and pneumococcal vaccines are strongly recommended for these patients, while live vaccines, such as yellow fever, should be avoided[83].

A major concern is that vaccinations may cause an exacerbation or progression of pre-existing autoimmune diseases. The risk/benefit evaluation of recommended vaccines in patients with autoimmune diseases is in favor of vaccination in most cases[83].

9. Conclusions

Vaccines have been studied and monitored over time in order to evaluate a possible link between vaccination and the onset of autoimmune diseases or immune-mediated phenomena. However, a causal link between vaccination and AEFI has been ascertained only for a few cases; moreover, AEFI are significantly lower after vaccination than those produced by infection with the wild microorganism, thus confirming the high safety profile of vaccines. Nevertheless, it is important to continue AEFI monitoring, especially for new vaccines, in order to evaluate the safety of vaccination, identify any potential signal and maintain confidence in immunization procedures[7][84].

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