International Immunopharmacology 20 (2014) 170–180

Contents lists available at ScienceDirect

International Immunopharmacology

journal homepage: www.elsevier.com/locate/intimp

Short review

Systemic immunotoxicity reactions induced by adjuvanted vaccines

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ARTICLE INFO

Article history:
Received 6 December 2013
Received in revised form 4 February 2014
Accepted 21 February 2014
Available online 6 March 2014

Keywords:
Systemic reactions
Adjuvant
Vaccine
Immunotoxicity
Action mechanisms

ABSTRACT

Vaccine safety is a topic of concern for the treated individual, the family, the health care personnel, and the others involved in vaccination programs as recipients or providers. Adjuvants are necessary components to warrant the efficacy of vaccines, however the overstimulation of the immune system is also associated with adverse effects. Local reactions are the most frequent manifestation of toxicity induced by adjuvanted vaccines and, with the exception of the acute phase response (APR), much less is known about the systemic reactions that follow vaccination. Their low frequency or subclinical expression meant that this matter has been neglected. In this review, various systemic reactions associated with immune stimulation will be addressed, including: APR, hypersensitivity, induction or worsening of autoimmune diseases, modification of hepatic metabolism and vascular leak syndrome (VLS), with an emphasis on the mechanism involved. Finally, the authors analyze the current focus of discussion about vaccine safety and opportunities to improve the design of new adjuvanted vaccines in the future.
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http://dx.doi.org/10.1016/j.intimp.2014.02.033
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1. Introduction

Vaccination remains an important public health tool for infectious disease prevention and more recently as part of the therapeutic arsenal against chronic diseases. The safety of vaccines is a priority, particularly in the prophylactic programs [1,2]. Recent advances in vaccine research have increased our understanding of the mechanisms by which vaccine components contribute to the immune response and also to several adverse responses [3,4].

Almost all the local and systemic toxicity induced by adjuvanted vaccine is of an immunotoxic nature. The types and impact of the local reactions were highlighted in a recent review [5]. Regarding systemic toxicity, apart from fever and other minor transient symptoms sometimes often referred to as "flu-like symptoms", the available data on the systemic side effects of vaccines are generally scarce, being regarded as rare events. Many of these are subclinical, requiring laboratory methods to be detected. However, the risk of a severe reaction in people suffering from other pathological or genetic conditions is unknown. Certainly, few studies have carefully evaluated the systemic reactions induced by adjuvants [6].

The main mechanism giving rise to toxic systemic effects after the administration of adjuvanted vaccines usually involves the hyperactivation of immunological mechanisms, often mediated by the release of proinflammatory cytokines, such as IL-1, TNF-β, IL-6 and IL-17, chemokines and other endogenous factors [7,8]. These early effects can trigger other secondary reactions in distant organs and tissues with different levels of graveness (Fig. 1). Other less well known mechanisms involving failure of a regulatory pathway, that can lead to systemic vaccine toxicity will be analyzed later.

Although it is accepted that adjuvants are the cause of many toxic reactions of vaccines due to overstimulation of the immune system, the vast majority of toxicity studies with adjuvants were performed in adjuvant + antigen formulations (experimental and clinical vaccines), with limited information regarding adjuvants alone, being a potential problem to understand all data published. In this review, several kinds of systemic reaction will be discussed, with an emphasis on the mechanisms behind the acute phase response (APR), hypersensitivity reactions, induction or worsening of autoimmune diseases (ADs), modification of hepatic metabolism (MHM) and vascular leak syndrome (VLS). Several of these reactions have been rarely observed in

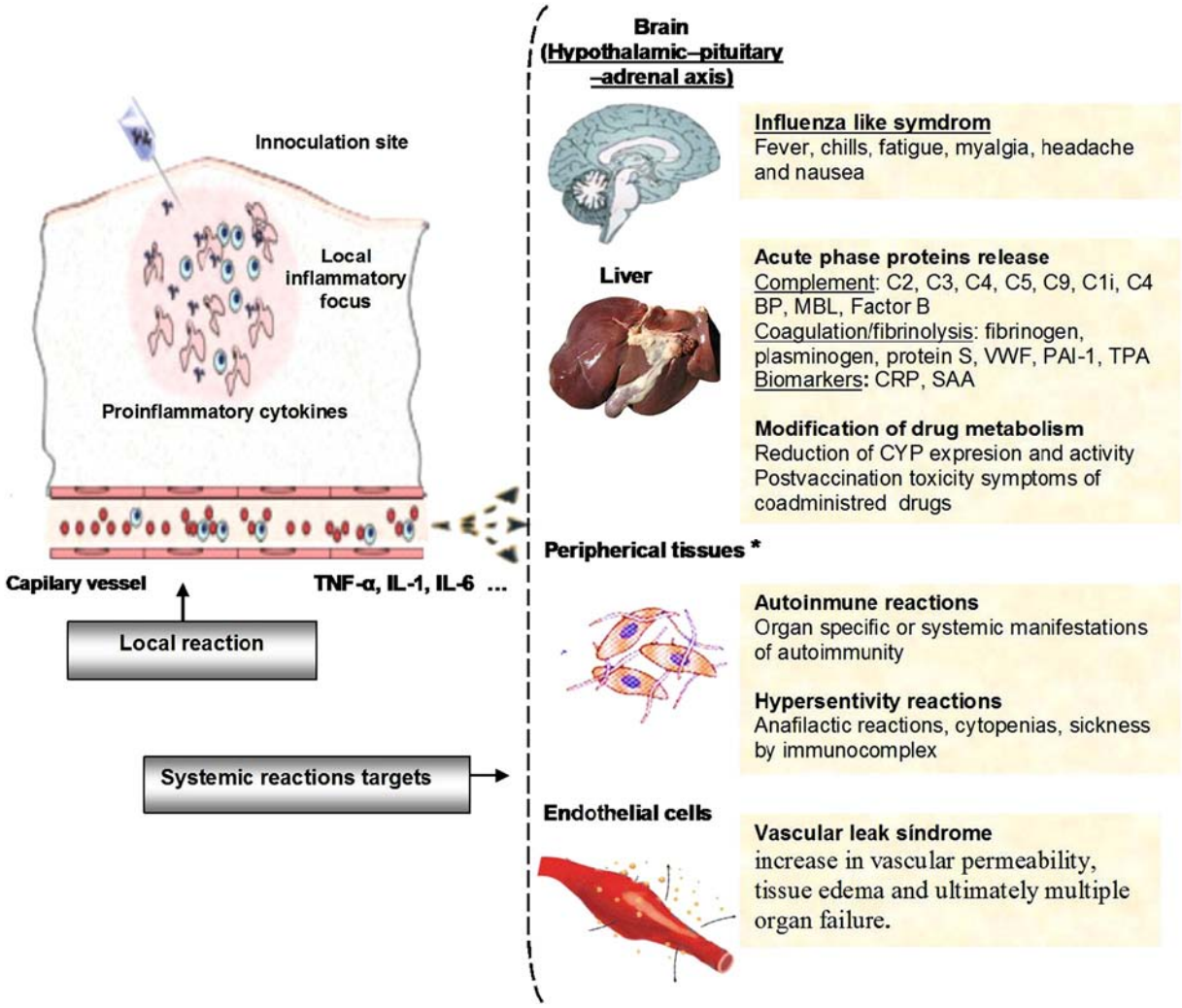

Fig. 1. Simplified overview of immunotoxic reactions induced by adjuvanted vaccines. After inoculation, the adjuvant can cause a local inflammatory focus initiated by danger signals contained in the vaccine itself or endogenous factors released by the local irritation. These early events promote the secretion of pro-inflammatory cytokines by the innate immune system, which consolidate the local reactions and, after subsequent transfer to the circulatory system, produce systemic manifestations of immunotoxicity in several organs or tissues. In the hypothalamic–pituitary–adrenal axis, the proinflammatory cytokines induce the influenza-like syndrome; in the liver, the release of acute phase proteins is stimulated and the activity of CYP is inhibited, affecting drug metabolism; various tissues may be affected by allergic or autoimmune reactions and the action in the endothelial cells can induce a VLS. Note: This figure depicts a theoretical extreme situation and is not representative of any particular adjuvant. Pathogen-Associated Molecular Patterns, PAMPs. *In autoimmune and allergic reactions, other mechanisms of the adaptive immune systems are involved that are not shown.

prophylactic vaccine or under special conditions (therapeutic vaccines, accidentally or in experimental models). In this article, embryo–fetal immunotoxicity is not discussed as it is dealt in another study.

2. Vaccine composition

Vaccines are composed of several ingredients that can influence the safety of formulations. The more important components of vaccine are the antigen, which guarantees its specificity, and the adjuvant, that ensures the potency and quality of the immune response. The antigen can be whole-cell microorganisms (either bacteria, viruses or fungus), attenuated or killed, or their subunits purified, recombinant or synthetic (proteins, peptides, carbohydrates, genetic materials). On the other hand, adjuvants are highly variable chemically in nature and mode of action, making it hard to generalize about their toxic effects, except in some local reactions of variable magnitude that they often induce [5].

Other components normally present in vaccines are diluents, preservatives and manufacturing residues. The function of these ingredients is to dissolve all the components and to avoid any further chemical reactions and decomposition or multiplication of the biological constituents of the vaccine. They are regarded as innocuous, but sometimes trigger allergy reactions in susceptible individuals.

3. Severity of vaccine adverse events

In terms of severity, vaccine adverse events can be classified into two types [9–11]: 1) non-severe adverse events: (i) local (pain, lump at the injection site, redness > 5 cm or other local events like pruritus or hematoma) that persist at least 48 h; (ii) regional (ulcer, lymph node tenderness and/or enlargement, adenitis, abscess at the injection site); and (iii) systemic (fever ≥ 38 °C or any event thought to be related to vaccination, with sick leave for more than two days); and 2) severe or serious adverse events: according to the 21 Code of Federal regulations serious cases are defined as one of the following outcomes: death, a life-threatening condition, hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity or a congenital anomaly/birth defect [12]. Other medically important conditions may be considered serious adverse events when, based upon appropriate medical judgment, they may place the subject at risk of requiring medical or surgical intervention to prevent one of the outcomes listed in this definition. Although at various points it will be necessary to refer to local reactions, this review focuses on the systemic postvaccination reactions.

4. Early events before systemic postvaccination reactions

The early events triggering systemic postvaccination reactions are initiated at the site of inoculation. These local reactions are consistently associated with severity of systemic reaction rates [13].

Naturally, invasion of a pathogen induces a rapid inflammatory response and, in the same way, immunization is followed by a local inflammation at the site of inoculation, releasing proinflammatory cytokines [5,7]. When these cytokines cross the capillary walls and enter blood circulation, they may reach distant sites, with effects on certain target cells (Fig. 1).

The stimulation of innate immunity is initiated by the interaction of highly conserved components of pathogens, called Pathogen-Associated Molecular Patterns (PAMPs) [14], or products released by damaged tissues, called Danger-Associated Molecular Patterns (DAMPs) [15,16], with receptors on immune cells named Pattern Recognition Receptors (PRRs). The recognition of these signals by PRR leads to the activation of intracellular pathways in innate immune cells. The activation of macrophages and dendritic cells (DCs) culminates in the expression of nuclear factor-κB (NF-κB) and IRF7 via MyD88/TIRAP or TRIF/TRAM, to induce inflammatory cytokines (TNF, IL-1, IL-6), chemokines (CCL2, CXCL8, others), endothelial adhesion molecules (E-selectin), co-stimulatory molecules (CD80, CD86) and type I interferon [17]. Expression of these molecules creates a local pro-inflammatory environment, where phagocytes are recruited and activated, leading to the activation of the complement cascade and chemoattraction of the effector cell adaptive immune response, while the invading pathogens are contained [18].

In adjuvanted vaccines, the adjuvants mimic signals induced by pathogens, activating the innate immune cells [19]. Most of the PAMPs used as vaccine adjuvants, such as monophosphoryl lipid A (MPL); flagellin and CpG oligonucleotides, are agonists of toll-like receptors (TLRs) [20], while others such as alum are TLR-independent adjuvants [21] (Fig. 1).

Cytokines used directly as immunological adjuvants [22,23] or for treatment of several diseases [24,25] are involved in the early phase of the immune response, but are involved directly or indirectly in the pathogenesis of immune-mediated disorders described in humans and animals [24]. Therefore, it is not surprising that strong immunostimulation mediated by adjuvants, associated with subsequent release of various cytokines, is also capable of producing manifestations, depending on their concentration [3,5,7].

5. General mechanisms involved in systemic immunotoxicity induced by adjuvanted vaccines

5.1. Profuse release of inflammatory cytokine

Adjuvants can over-stimulate the inflammatory mechanisms, with high production of TNF and other mediators, such as: tumor necrosis factor-alpha (TNF-α), interleukin 1 beta (IL-1 β), IL-2 and IL-6. They can generate a variety of symptoms, according to the quantity and the time they last in the plasma, ranging from a transitory hyperthermia to a state of shock, with danger to life, similar to that observed in sepsis [26]. In 2006, a severe reaction was reported during the Phase I clinical trial of TGN1412, a therapeutic CD28-specific monoclonal antibody (mAb), developed for the treatment of rheumatoid arthritis, leukemia and multiple sclerosis; instead of the intended pharmacologic effect, it caused near fatal reactions in all 6 healthy volunteers. Within 2 h of receiving a single intravenous dose of 0.1 mg/kg vw, all six volunteers had a systemic inflammatory response, characterized by a rapid induction of pro-inflammatory cytokines. Within 16 h, all six volunteers became critically ill with acute lung injury, multiple organ failure, and disseminated intravascular coagulation that would result in amputation of the fingers and toes for the worst affected. This newly observed phenomenon was termed 'cytokine storm' [27]. The mechanism of cytokine release caused by TGN1412 seems to be different from that caused by other therapeutic mAbs, because it involves a different arm of the immune system, the CD4+ effector memory T-cells, but activation of the other arms of the immune system also has the potential to cause a 'cytokine storm' [28]. This raised an alert about the consequences of strong stimulation of the immune system and the need of major effort to develop preclinical assays for prediction of these consequences [28]. Several consequences of high plasma levels of proinflammatory cytokines following vaccination will be analyzed in the following sections.

5.2. Off-target effect

The current data indicate that not only immunity is regulated systemically, but also each organ has distinct patterns of expression of certain immune molecules, allowing an accommodation of the immune mechanism to the characteristics of the organ [29]. This implies expression of receptor-like PRR on cells other than the classic innate immune cells, to function in regulating their microenvironment [29–32]. This expression can be either constitutive or inducible. TLR4 is expressed by human vascular smooth muscle cells [33], while various TLRs are present in the female reproductive tract in humans [34], non-immune liver cells [31], and intestinal epithelium [30,32], and TLR2 can be induced in the liver after intraperitoneal injection of Freund's adjuvant [35].

The term "off-target effect" was used by Hauguel and Hackett to refer to inflammation induced by adjuvants in non-immune tissues able to express innate immune receptors like TLRs. Although the TLR expression in non-immune cells seems to play a regulatory role [29,31] it is possible that TLR agonist adjuvants might induce undesirable inflammation, even autoimmune reactions, in sensitive tissues under certain conditions and in susceptible organisms [36,37]. More research is required to determine the possible role of these mechanisms in systemic toxicity of adjuvanted vaccines.

5.3. Suboptimal downregulation of the innate immune system activation

The initial activation of the innate immune system constitutes the first step toward the subsequent activation of adaptive immunity. Once the activation of adaptive immunity begins, multiple pathways of negative feedback inhibit innate immunity, thus avoiding an unbridled activation of inflammatory cascades harmful to the organism. This process is named transition from innate to adaptive immunity [38]. Failure in this homeostatic mechanism is seen as a potential source of adjuvant toxicity [37]. Although this feedback control system is not fully understood, several of its pathways have been described. For example, the cytokine IL-21, produced by activated T cells, may initiate immunosuppressive activity in dendritic cells (DCs) and diminish natural killer (NK) cell responses while stimulating adaptive immune responses [39,40].

5.4. Failure in the contraction of adaptive immune response

Just as innate immunity is controlled to avoid an excessive inflammatory response, so is adaptive immunity also regulated. An effective immune response eliminates the microbes that initiated that response. This is followed by a contraction phase, in which the expanded lymphocyte clones die and homeostasis is restored, allowing the immune system to recover from one response and return to a state of rest after eliminating each foreign antigen, thus keeping ready to respond to other antigens [41]. Regulatory T-cell immune responses are driven by various types of immune cells. T regulatory cells, expressing CD25 (the interleukin-2 (IL-2) receptor α-chain), have the ability to suppress the activation, proliferation and effector functions of a wide range of immune cells, including CD4+ and CD8+ T cells, natural killer (NK) and NKT cells, B cells and antigen-presenting cells (APCs) [42–44]. This unique ability to control immune responses makes FOXP3+ Treg cells central to the prevention of autoimmunity, allergy and other immunopathologies that can appear after a persistent and uncontrolled specific immune response [44,45]. Other cells, such as plasmacytoid DCs, also regulate B cells via interferon production and direct cell interaction thus modulating their activation, mediated by TLR stimulation and controlling possible antibody-mediated autoimmunity [46].

5.5. Loss of peripheral immunotolerance

Together with responsiveness to foreign antigens, tolerance to self-antigens is crucial for the maintenance of the immune system. Immunotolerance can be central, when it is developed in the primary immune organs, bone marrow and thymus, triggering deletion of autoreactive lymphocytes; or peripheral, occurring after the maturation of lymphocytes away from the primary organs in various ways, including: clonal anergy, ignorance, abortion and others [47,48]. Strong adjuvants are able to break peripheral tolerance by several mechanisms [49,50].

5.6. Excessive Th2-biased response

The development of Th2 responses against antigens is a malfunction of the adaptive immune system, with excessive production of IL-4 and several other cytokines, including IL-13, IL-18, IL-25 and IL-6 with high production of IgE. This dysfunction of the immune system may result from false alarms generated by the innate immune system, resulting in unexpected dendritic cell (DC) maturation after exposure to allergens. Conditions in the local microenvironment during DC maturation may also result in the preferential induction of Th2 responses [51]. Once IgE is produced, it binds with high affinity to Fce RI on mast cells, basophils, and other cells expressing lower levels and various forms of Fce RI, and after subsequent encounter with the same antigen, it activates signal transduction pathways that regulate secretion and other functions of mast cells and basophils, inducing an allergic inflammation [52].

5.7. Formation and deposition of immune complex

Antigen–antibody complexes are normally produced during immune responses. Such complexes typically produce severe and long-lasting tissue injury only when they are produced in excessive amounts, are not efficiently cleared, and become deposited in tissues. The deposition of immune complexes in vessel walls leads to complement and Fc receptor-mediated inflammation and injury to the vessels and adjacent tissues [53]. Two reactions mediated by immune complex are associated to vaccination procedures. "Serum sickness" is produced by immunization with a large dose of a foreign protein antigen or multiple injections of antigen, which lead to the formation of immune complexes, that are deposited most often in the kidneys, arteries, and lungs. The "Arthus reaction" is a localized form of immune complex-mediated vasculitis, induced by injection of an antigen subcutaneously into a previously immunized individual with high titers of antibodies or an animal that has been given intravenous antibody specific for the antigen [53,54].

6. Main syndromes associated with systemic toxicity of adjuvanted vaccines

6.1. Acute phase response (APR)

APR is a transient syndrome that develops in response to an injury. It is mediated by pro-inflammatory cytokines and is characterized by local inflammatory response and a systemic component. This includes leukocytosis, production of acute phase proteins by hepatocytes, fever and various changes in lipid, protein and carbohydrate metabolisms that accompany typical side effects seen during infections, certain immunotherapeutic regimens, fatigue and anorexia [55,56].

Flu-like symptoms (FLSs) are observed in APR, commonly associated with vaccination with attenuated or killed bacteria or adjuvanted vaccines, as an expression of hyperstimulation of the immune factors [57]. FLS usually appears within hours of the administration of an immunostimulating drug or vaccine, and recedes within a few hours without complications. FLS typically consists of fever, chills, fatigue, myalgia, headache and nausea. Fever of varying magnitudes is characteristic of patients with FLS, ranging from a moderate increase in body temperature (38–39 °C) to marked hyperpyrexia, exceeding 40 °C in some cases [58]. IL-1, released by leukocytes, and other endogenous factors (IL-1β, TNF- , IFN-β, IFN-γ, IL-6, IL-8), along with macrophage inflammatory protein-1, act as pyrogens and are the main agents responsible for these reactions [59].

Pro-inflammatory cytokines, overflowing into the systemic circulation, can gain access to the brain through saturable transport systems, and enter the circumventricular organs through fenestrated capillaries, where they induce the production of prostaglandins, such as PGE2, a centrally controlled mediator of fever. Synthesis of PGE2 depends on cyclooxygenase (COX) activity, while the induction of COX-2 in response to peripheral injection of a fever-inducing dose of LPS was demonstrated in the brain endothelial cells, perivascular microglia and meningeal macrophages [56,58,60]. PGE2 is produced in response to activation via the hydrolysis of membrane-associated phosphoinositide by phosphoinositide-specific phospholipase C, activated

by the complement cascade [58], and adjuvant as a component of vaccine is a determining factor in production [61].

A recent study evidenced that the serum level of TNFα, a key mediator of APR, and the production of TNFα by lympho/monocytes in response to LPS stimulation are very variable in different members of a healthy human population, also suggesting that high individual variations exist in response to infections [62]. In this way, although FLS is one of the more common side effects post-vaccination, not many studies focus on the impact of immunization on diverse mediators involved in APR [7,63–65].

6.2. Hypersensitivity reactions

Hypersensitivity, frequently called allergic reaction, can be the cause of certain local or systemic reactions observed following vaccination. The classic Gell and Coombs classification lists four types of hypersensitivity reactions, namely anaphylaxis (type I), antibody-mediated cytotoxic reactions (type II), immune complex-mediated reactions (type III), and delayed hypersensitivity (type IV). Although this classification was proposed more than 40 years ago, it is still widely used as an aid to understanding immune reactions, even though it does not in itself fully explain all immune-related phenomena [66].

From a clinical viewpoint, the type I hypersensitivity reaction, also known as immediate hypersensitivity and anaphylactic allergy, is the most serious vaccine-associated reaction. It is normally caused by specific IgE antibodies, resulting from a previous sensitization to one of the constituents of a vaccine: the infectious agent or one of its products; adjuvant: aluminum hydroxide; stabilizer: gelatin; preservatives: thiomersal; antibiotic: neomycin; biological culture medium: chicken embryo cells; or a latex stopper on the vial (falta uma).

Anaphylaxis is characterized by three factors: 1) the clinically apparent onset from 10 to 20 min after exposure to the agent in question; 2) the rapid sequence of symptoms that reflect a serious life-threatening condition; and 3) the reversibility of the situation resulting to appropriate treatment. The intensity of the manifestations of anaphylaxis varies from generalized urticaria with erythema and pruritis to most severe cardiovascular and respiratory symptoms with shock, bronchoconstriction and laryngeal edema. Sometimes, isolated urticaria is observed within 24 h of vaccination, which must nevertheless be considered a possible manifestation of a type I allergic reaction, even though other types of immune reaction may be the cause of this skin rash. The gastrointestinal tract may become involved, with non-specific symptoms such as incontinence, vomiting, abdominal pain and diarrhea. The central nervous system can be also affected, including a feeling of impending doom and unconsciousness, probably related directly to hypotension and hypoxia [67]. Rüggeberg et al. updated the case definition of anaphylaxis and the guidelines for data collection, analysis and presentation of immunization safety data [68].

Regarding the frequency of these reactions, many studies show that it is of low frequency. For example, in New Zealand a large study over a 5-year period on 15 marketed vaccines revealed an estimated rate of 1 immediate hypersensitivity reaction per 450,000 doses of vaccine administered. Another large study, conducted within the Vaccine Safety Datalink, described a rate of reaction from 0.65 to 1.53 cases per million doses. Although these per-dose estimates suggest that true hypersensitivity reactions are quite rare, the large number of doses that are administered, especially for the commonly used vaccines, makes this a relatively common clinical problem [69].

In rare circumstances, certain vaccines may cause acute exacerbation of allergic diseases, but the argument that vaccination causes allergic disease is not still substantiated by any available evidence [70]. Furthermore, there are no data supporting an association, provocative or protective, between receipt of the BCG, DTP or whole-cell pertussis vaccine and a risk of asthma in childhood and adolescence [71–73].

Even more controversy exists about the possibility that the impact of vaccination on the prevalence of atopic diseases has increased sharply in the past few decades, especially in children 0–4 years old; as hereditary factors cannot account for this increase, there is a search for environmental factors that could promote atopy, including vaccination [4,74]. The search for the real relationship between vaccination and atopy, at the population level, will require rigorously standardized studies with larger populations, including unvaccinated subjects and a previously unrecognized sub-population genetically vulnerable to the T-helper (TH)-2 immune response [4,75].

The question of adjuvant-induced allergy is controversial. The general ability of aluminum adjuvants to stimulate the production of IgE as part of the overall Th2 profile and increase eosinophilia is well established. However, in practical conditions, it has been difficult to demonstrate cases where vaccination with aluminum adjuvants has led to IgE-mediated allergy toward the vaccine antigen [76]. Recently, descriptions of the underlying mechanism of aluminum adjuvanticity [77–79] and how aluminum adjuvants could promote and enhance non-target IgE synthesis in a genetically vulnerable person [4] have been published. Aluminum increases inflammasome activity, promoting the release of IL-1β, IL-18, and IL-33, but not IL-12, thus leading to a Th2 profile, characterized by further release of IL-3, IL-4, IL-5, IL-9, and IL-13, and IgE-potentiating factors such as sCD23. Furthermore, it stimulates macrophages to produce PGE2, which also participates in regulating immune responses. The response to aluminum-containing vaccines in children and their association with allergic reactions depend on the various genetic variants of cytokines, such as IL-4, IL-13, IL-33, and IL-18, defining a genetically vulnerable sub-population [4].

Type II hypersensitivity reactions are cytotoxic or cytolytic reactions. In these reactions, cytotoxic antibodies recognize an antigen that has attached itself to the membranes of certain cells, forming a combined antigen. These antibodies cause the destruction and lysis of the cell. These reactions are linked primarily to medication-related cytopenia and to blood transfusion injuries resulting from incompatibility. There are sporadic reports of anemia and thrombocytopenic purpura after recombinant hepatitis B vaccine, with possible involvement of type II hypersensitivity [80–82].

Type III hypersensitivity includes reactions resulting from the formation of immune complexes, by combination of an antigen and an antibody, which in turn cause an intense inflammatory reaction, leading to tissue damage. The soluble antigen–antibody complexes can be deposited either locally (to form an Arthus reaction) or be systemically distributed, causing “serum sickness”. The Arthus reaction begins from 2 to 8 h after the injection of an antigen and causes massive, painful swelling of the limb [83]. On the other hand, “serum sickness” includes symptoms such as fever, arthralgia and rashes, which are often urticarial and are observed after the administration of high levels of foreign-source antibodies (e.g., horse serum to treat tetanus) [54,84].

Type IV reactions are not produced by antibodies, but by Th1 lymphocytes. These reactions are characterized by a delay of 24 to 72 h before the appearance of manifestations, following the introduction of the antigen into the organism, and are restricted to local inflammation at the injection site that can develop as far as a granuloma and local necrosis [83].

6.3. Induction or worsening of autoimmune diseases

Experimentally, it is easily possible to induce an autoimmune disease in genetically susceptible laboratory animals, by immunizing them with a formulation containing a strong adjuvant (e.g. FCA) and an autoantigen [85–87].

In clinical practice, there are numerous reports of suspicions of autoimmune diseases induced by vaccines [88–95]. These reactions have been attributed principally to the presence of adjuvants [50,92,95–97] and, just recently, an autoimmune/inflammatory syndrome induced by adjuvants (ASIA) has been proposed [98] (Table 1). In addition, some animal models have been developed to seek experimental evidence of the clinical suspicions [95,99–102]. Despite the mounting

Table 1
Suggested criteria for the diagnosis of ASIA.
Source: J. Autoimmun 2011; 36: 4–8. Reproduced with permission from the authors.

Major criteria
● Exposure to an external stimulus (infection, vaccine, silicone, adjuvant) prior to clinical manifestations
● The appearance of "typical" clinical manifestations:
✓ Myalgia, myositis or muscle weakness
✓ Arthralgia and/or arthritis
✓ Chronic fatigue, non-refreshing sleep or sleep disturbances
✓ Neurological manifestations (especially associated with demyelination)
✓ Cognitive impairment, memory loss
✓ Pyrexia
✓ Dry mouth
● Removal of inciting agent leads to improvement
● Typical biopsy of organs involved
Minor criteria
● The appearance of autoantibodies or antibodies directed at the suspected adjuvant
● Other clinical manifestations (irritable bowel syndrome)
● Specific HLA (HLA DRB1, HLA DQB1)
● Development of an autoimmune disease (multiple sclerosis, Sjögren's syndrome, SLE)

evidence, there still persists a great polemic, since several epidemiological studies have not confirmed the existence of an unequivocal causal relationship [97,103–105,106,107].

For the epidemiological studies, the three following questions should be addressed when suspecting a link between vaccines and autoimmunity: is a specific vaccine associated with the development of a new unique autoimmune disease?, does a particular vaccine increase the risk of any autoimmune disease in some predisposed individuals? and can a vaccine be safely administered to a patient who is suffering from a known autoimmune disease? [103].

In theory, a classical vaccine formulation contains the necessary elements for a possible induction of autoimmune diseases in susceptible individuals [108]. The antigen may contain mimetic epitopes with self-structures, while the adjuvant stimulates the up-regulation of co-stimulatory molecules and other products of inflammation, leading to the polyclonal activation of autoreactive T cells [49,50,108]. This bystander activation can wake up anergic autoreactive lymphocytes, reviving their potential to trigger autoimmune reactions [3,109]. Furthermore, in the last decade, the role of innate immune activation and the importance of TLR signaling in T cell-driven autoimmunity have been investigated. It is accepted that given an inflammatory focus releasing high concentrations of proinflammatory cytokines and in the presence of TLR-agonists, T cell regulatory function may be abrogated and/or polyclonal effector T cell populations (including self-reactive T cells) might be expanded. The previous recognition of the specific antigen, with low affinity or in the absence of costimulation, could now receive alternative costimulation via TLR ligation and thus increase the strength of signal received by self-reactive T cells, unleashing their effector function against self [36,110].

Autoantibodies are a hallmark of autoimmune diseases. A transient post-vaccination elevation of autoantibodies in the serum without obvious clinical significance has been described in patients with various autoimmune diseases and in healthy animals [111–113]. However, very few data exist of an increased level of autoantibodies or the appearance of new autoantibodies in healthy persons after immunization. Recently, cases of production of autoantibodies following vaccination with recombinant hepatitis B and influenza vaccines have been reported in humans [114]. The relevance of this subclinical effect requires more detailed study.

Finally, consistent with the fact that vaccine-induced autoimmunity is indeed rare, some genetic pattern could be a predisposing factor in determined subjects, in which antigen presentation, influenced by certain HLA haplotypes such as HLA-DRB1 and DQB1, can lead to the autoimmune cascade after vaccination [98,115,116]. Thus, pre-existing risk factors, including genetic predisposition and even environmental factors, are largely accepted as being involved [117]. Fortunately, the immune system has numerous regulatory mechanisms, and naturally re-establishes the normal balance of adequate response versus over-response.

In spite of experimental and clinical reports of suspected or demonstrated association between hyperstimulation of the immune system and autoimmunity, and the elucidation of some possible mechanisms, the evidence of vaccinations inducing or worsening autoimmune disease remains unclear, highlighting the need for more research to understand the possible role of adjuvants and vaccines in triggering autoimmunity in clinical practice.

6.4. Modification of drug hepatic metabolism

Reports of patients developing phenytoin, warfarin or theophylline toxicity, following acute infections [118,119] and anti-influenza vaccination, have been published [119–128]. In one study, toxic elevations in the levels of the concurrent medicines were reported to occur up to 28 days after vaccination [124]. Other vaccines such as Bacillus Calmette Guerin (BCG), and immunostimulators such as interferons and various cytokines are able to produce the same effect [129–131]. The effect of immunostimulation on drug metabolism was demonstrated several decades ago in laboratory animals, using several vaccines and adjuvants, with the demonstration that cytochrome P450 hepatic enzyme inhibition as a consequence immunostimulation is involved, leading to reduced clearance of the concurrently administered medicines [132–135]. Years later, Renton reported that the release of cytokines, such as IL-1, IL-2, IL-6, TNF, TGF-β and IFNs, is involved in modulating the expression of several P450 isoforms [130]. Reversible changes in the pharmacokinetic parameters of theophylline, and decreased expression of CYP1A, 2B1/2, and 3A subfamily, have also been reported in rats after intravenous injection of lipopolysaccharide (endotoxin) derived from *Klebsiella pneumoniae* [136] and a similar effect was observed after application of FCA to mice (used as a positive control), for comparison with a non-toxic intranasal adjuvant called AFCo1 [97].

On the other hand, Prandota have shown the rapid decrease in the total CYP450 liver content of FCA-treated rats and the selective down-regulation of specific CYP isoforms through a direct reduction in mRNA levels (CYP2B, CYP2CI1, CYP3A1, and CYP2E1), protein content (CYP2B, CYP2C11, and CYP2E1) and catalytic activity (CYP2C6, CYP2C11, and CYP2E1). Thus, Prandota has highlighted that polymorphisms of drug-metabolizing enzymes and cytokines may contribute markedly to drug-induced hepatotoxicity and drug pharmacokinetic disturbances, affecting genetically predisposed subjects [137].

These reports reveal a real risk of vaccination, in older patients or susceptible people suffering from various chronic diseases, affecting drug metabolism, for example in chronic hepatitis or hepatic cirrhosis with concomitant administration of drugs such as theophylline, carbamazepine and warfarin. Fortunately, this reaction is reversible and, except in some specific serious cases, does not preclude the use of vaccination, but physicians should observe the patients closely after vaccination. Certainly more research is necessary, monitoring other drugs after vaccination, to know their specific pharmacokinetic profile under various clinical conditions.

6.5. Vascular leak syndrome (VLS)

Several cytokines have been tried as valuable adjuvants. They can be used either systemically or mucosally in different types of vaccines. Some of the experiments in which cytokines were used as vaccine adjuvant include TNF-α for mucosal vaccine against HIV [138]; type I IFN as adjuvant in an anti-influenza vaccine [139,140] and hepatitis B vaccination [141]; granulocyte macrophage colony-stimulating factor (GM-CSF) as an adjuvant for hepatitis B vaccination [142], HIV-1 vaccination [143] and in anticancer vaccine [144–146]; interleukin-12 (IL-2) as a mucosal adjuvant for vaccination of humans to protect against

respiratory pneumococcal infection [147–149]; interleukin-15 (IL-15) in antituberculosis vaccine [150,151], in antitumor vaccine [152] or in anti-HIV-1 [153]; and interleukin-22 (IL-22) in HBV DNA vaccination [154].

VLS is a major dose-limiting effect seen after administration of several cytokines, such as: IL-2 [24,155–157], IL-1 [158], IL-3 [159], IL-4 [160,161], GM-CSF [162,163], interferon (IFN)-α [164] and IFN-β1b [165]. VLS is characterized by an increase in vascular permeability resulting in tissue edema and, ultimately, multiple organ failure. Manifestations of VLS include increased body weight, hypotension, fluid shifts, peripheral edema, pleural and pericardial effusions and ascites. In severe cases, VLS-related conditions may progress to pulmonary and cardiovascular failures [166]. The pathogenesis of vascular damage is complex and poorly understood and can involve activation of endothelial cells and leukocytes, release of cytokine and inflammatory mediators, alteration in cell–cell and cell–matrix adhesion with disturbance of vascular integrity, activation of components of the complement cascade, as well as alterations in cytoskeleton function resulting in disturbance of vascular integrity [166,167]. There have also been reports of the effect of lymphokine-activated killer (LAK) cells on vascular endothelial cells, with the development of VLS [167] involving perforin, Fas ligand and CD44, observed in gene-targeted mice [168,169]. The observation of VLS is a serious obstacle to the clinical use of cytokines as adjuvants in vaccines [3,170].

6.6. Oral immunosuppression or tolerance postvaccination

Oral administration of antigens induces systemic unresponsiveness termed oral tolerance. It is a suppressive mechanism to prevent the host immune system from overreacting to innocuous antigens, but this effect has been often described after oral administration of vaccines. Some adjuvants can induce immune deviation and immunosuppression involving down-modulating an existing immune response for therapeutic benefit [171]. This approach has been explored for the control of two noninfectious classes of disease: allergy and autoimmunity. Therapeutic vaccines against these diseases may involve switching the immune response from one type to another, for example deviation of Th2 to Th1, or suppressing an immune response by the induction of Tregs [45,171]. The development of an antigen-specific Treg inducing vaccine is a major novel goal in the field of immunotherapy against autoimmune diseases and the use of a Treg inducing adjuvant might be required to achieve an effective regulatory response [45].

Just as an adjuvant can be used for therapeutic immunosuppression, this effect can appear as an undesirable effect. Once oral tolerance is induced it is sufficiently robust that subsequent exposure to that antigen, even via a systemic route, suppresses immunity [172,173]. The mechanisms involved in oral tolerance induction and effects are complex and not fully defined, but the main mechanism involves the generation of suppressor-regulatory T cells [174].

7. Impact of doses and route of administration

The influence of the doses and the route of administration in adjuvanted vaccine toxicity has been revised [3,83] and the data available are principally referred to local reactions, although, as was already mentioned before, the severity of local reactions may be associated to proportional systemic manifestations [13]. With exception of undesirable tolerance frequently induced after oral vaccination, adjuvanted vaccines administered mucosally (intranasal, oral, sublingual, rectal, vaginal) or transcutaneously, seem to be less toxic for systemic reactions than parenteral vaccination [175]. Interestingly, different cytokines such as: TNF, type I interferon, IL-1, IL-12 and others that are mediators or systemic reactions, were safe and effective when administrated with antigens as mucosal adjuvants [22,138–140,148,175].

8. Non-immunological adverse reactions

Several postvaccination events are often registered but are not regarded of immunotoxic nature. They are principally of infectious, traumatic and psychological origin. Acute infections at the site of inoculation can be produced by injection of a previously contaminated product or due to lack of meticulous attention to sterile technique and disinfection before injection, local abscesses often being produced by Group A *Streptococcus* and *Staphylococcus aureus* [204,205]. On rare occasions it is reported that a vaccine caused the same infectious disease against which it was made, owing to problems of attenuation or in a patient with severe immunodeficiency. For this reason, attenuated vaccines are limited in these patients [206].

Frequently, there are reports of symptoms associated with vaccination that are of a psychological nature, with vasovagal reactions: hypotension, vertigo, syncope, vomiting and other digestive symptoms, fatigue, and cardiac arrhythmia [10,11].

9. Final considerations

Undoubtedly the future development of vaccines is dependent on the use of adjuvants. The most important attribute of any adjuvanted vaccine is that it be more efficacious than the aqueous vaccine, and that this benefit outweighs its risk. More than 90% of the adverse events reported correspond to mild or moderate local reactions and symptoms belonging to APR. Generally, grave reactions are of very low frequency or rare. This, together with the lack of understanding of the toxicity mechanisms and some difficulties with methods of assessment, stimulates several controversies over safety vaccination. Few studies have carefully evaluated systemic reactions to adjuvanted vaccines, including the role of the various cytokines [6,7]. One reason for this is that some reactions can occur subclinically (e.g. inhibition of drug metabolism) or can appear a long time after vaccination under the influence of other factors, limiting the possibility of establishing a causal relation, as happens with delayed autoimmune reactions, so that it is hard to define if a reported effect was caused or exacerbated by vaccination or not. Many vaccine safety studies have used the temporal association of immunization as part of the case definition of the event itself. When the reaction occurs rapidly after vaccination, with a time interval of just a few minutes between onset and exposure, there is often little doubt as to the cause of the event. However, delayed anaphylactic or autoimmune events are theoretically possible. In the first cases for example, as an atypical biphasic reaction, when a certain delivery system is used, involving the release of a depot or the delayed metabolism of a vaccine, a reaction might occur late after delivery of the vaccine [207]. Consequently, the temporal relationship between vaccination and a new diagnosis on the day of vaccination can be difficult to discern [208].

Another problem in the recording of postvaccination adverse events is that the basis for the detection of these reactions is under passive vigilance, in which the actual patient or parents voluntarily report the symptoms. Frequently, these reactions are not reported and, if they occur several days later, possibly nobody will find a causal relationship, and the event goes unrecorded. Thus, reliable and well-defined incidence rates cannot be derived from passive reporting systems used in post-marketing surveillance. There is a need for large and prospective multinational studies to arrive at a better understanding of the frequency and true nature of these rare events. Only by providing robust data can we expect to reliably assess vaccine safety and maintain public confidence in our immunization programs [207].

Table 2 summarizes the different factors associated with the occurrence of adjuvanted vaccine toxicity. Undoubtedly, the type of adjuvant used in the vaccine formulation [3,37] and individual susceptibility to adverse reactions, related to genetic differences [98,108,115,137, 194–196,209], are two of the more important aspects that, at the present time, are receiving most attention with regard to vaccine safety. Recently, Poland proposed the term “adversomics” to analyze vaccine

Table 2
Factors associated with the occurrence of adjuvanted vaccine toxicity.

Factors	Commentary	Selected references
Dependent on the vaccine formulation and procedures		
Type of adjuvant	The nature and mechanism of adjuvant are determinant in the balance between adjuvanticity and toxicity. E.g. oil emulsions induce local reactions, PAMP adjuvants such as LPS lead to APR and cytokines trigger VLS	[5,37,176]
Antigen	Antigen can favor autoimmunity (molecular mimicry) and allergy	[49,108,177,178]
Route and site of administration	The route of administration often determines the local and systemic side effects. The subcutaneous route is more reactogenic than intramuscular. Correct placement of the injected vaccine into the deep muscular layers decreases the local reactions. Local reactions, notably pain and swelling, are less common when the injection is given in the buttocks than in the thigh and in the arm. No injection site is consistently associated with lower systemic reaction rates. Mucosal vaccination is regarded as safer than parenteral, though Bell paralysis (for the intranasal route) and oral tolerance have been described.	[6,13,179–184]
Doses and booster	Low or high doses of vaccines lead to failure in the immune response. Short intervals of administration of the same or different vaccines can determine severe local and systemic toxicity.	[13]
Quality during production or conservation	Contamination of the vaccine at the time of formulation with reactogenic chemicals and microbial products; instability of the vaccine on storage with breakdown into reactogenic side products.	[6]
Dependent on the host		
Age	Vaccination at extreme age favors specific toxic manifestations, such as allergy in babies and drug toxicity by concomitant immunization with anti-influenza vaccine in older people. It is suggested that vaccines administered at birth can decrease the risk of developing diabetes mellitus, whereas primary vaccination after 2 months of age increased the risk of diabetes mellitus.	[184–188]
Gender	Some reports have suggested that the incidence of local or systemic reactions after influenza vaccination is higher in adult females than in adult males, although there is no definite conclusion of the value of this criterion for prognosis. Perhaps the main association might be with autoimmune diseases that are more frequent in woman. More studies are necessary.	[189–193]
Genetic background	Individual differences in vaccine effectiveness and susceptibility to adverse reactions are determined by HLA, TLRs and other genes. The term "adversomics" refers to vaccine adverse side effects at the molecular/genetic/proteomics level, identifying genetic characteristics associated with definable risks for specific serious vaccine adverse events. This includes susceptibility to allergy, autoimmunity, drug metabolic capacity and other reactions.	[98,108,115,194–196,209]
Personal pathologic antecedents	Live attenuated vaccines are contraindicated vaccines in immunodeficient patients or those under immunosuppressive treatments. Vaccination of patients with chronic diseases can lead to toxic manifestation such as local infection (site of injection) in diabetics, allergic manifestation in atopic individuals, disturbances of drug metabolism and chronic hepatitis.	[197–200]
Dependent on external factors		
Environmental factors	Several reports warn that environmental factors such as contamination might facilitate the induction of autoimmune diseases postvaccination. More research is necessary.	[201,202]
Interval of observation in immunization safety research	Postvaccination toxicity reactions can appear within the first hours or after days but others such as autoimmune reactions may be observed after month or years depending on the action of various factors. This is a current challenge in vaccine safety studies.	[117,201,203]

adverse side effects at the molecular/genetic/proteomics level, to identify genetic characteristics associated with definable risks of specific serious vaccine adverse events [195], and "vaccident" to include those unpredictable, accidental side effects that occur after receipt of a vaccine [196].

Although it is very difficult to warrant the absolute safety of an adjuvanted vaccine, the current advances in the knowledge of how innate immunity and immune regulation work, and about the mechanisms of adjuvant immunotoxicity [3], can contribute to a more rational design of vaccine, thus reducing the risk of toxicity and increasing efficacy [5,37,210]. The use of well characterized adjuvants and the introduction of new tools for a better evaluation prior to clinical trials, e.g. bioinformatics, in vitro models, molecular immunotoxicology methods, relevant animal models, and translational studies using relevant and sensible biomarkers, are today the important focus of attention in vaccine research [211–215].

In the near future, it is highly likely that individual patient genomes are readily available and routinely analyzed and these data can be used to predict a high risk of grave reactions [196]. This personalized vaccinology would allow the clinician to define the need for a given vaccine, the likelihood of developing a protective immune response, the number of doses needed and perhaps even what type of vaccine formulation would be necessary for a given individual.

Acknowledgments

The full content of this review was presented as part of the First Course of Immunotoxicity of Biological Products, for the Program of Biosciences and Biotechnology Applied to Pharmacy, held in February of 2013, in the Faculty of Pharmaceutical Sciences, UNESP Araraquara, SP, Brazil. The authors are grateful for the support granted by the UNESP and CAPES.

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