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Safety of vaccine adjuvants: Focus on autoimmunity

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ABSTRACT

Questions have been recently raised regarding the safety of vaccine adjuvants, particularly in relation to autoimmunity or autoimmune disease(s)/disorder(s) (AID). The International Life Sciences Institute (ILSI) Health and Environmental Sciences Institute (HESI) formed a scientific committee and convened a 2-day workshop, consisting of technical experts from around the world representing academia, government regulatory agencies, and industry, to investigate and openly discuss the issues around adjuvant safety in vaccines. The types of adjuvants considered included oil-in-water emulsions and toll-like receptor (TLR) agonists. The state of science around the use of animal models and biomarkers for the evaluation and prediction of AID were also discussed. Following extensive literature reviews by the HESI committee, and presentations by experts at the workshop, several key points were identified, including the value of animal models used to study autoimmunity and AID toward studying novel vaccine adjuvants; whether there is scientific evidence indicating an intrinsic risk of autoimmunity and AID with adjuvants, or a higher risk resulting from the mechanism of action; and if there is compelling clinical data linking adjuvants and AID. The tripartite group of experts concluded that there is no compelling evidence supporting the association of vaccine adjuvants with autoimmunity signals. Additionally, it is recommended that future research on the potential effects of vaccine adjuvants on AID should consider carefully the experimental design in animal models particularly if they are to be used in any risk assessment, as an improper design and model could result in misleading information. Finally, studies on the mechanistic aspects and potential biomarkers related to adjuvants and autoimmunity phenomena could be developed.

1. Introduction

Vaccines play an important role in modern medicine in the prevention of diseases. Safety is paramount, as vaccines are often given prophylactically to healthy individuals. Most vaccines work under the basic premise that the immune system becomes primed from a possible future exposure upon vaccination, therefore, providing protection to an individual. In the case of highly purified subunit vaccines that lack intrinsic innate immune activators (natural adjuvants), various types of adjuvants are added during formulation to assist in a better education of the immune system, and thus, provide better protection for any future insult. Developing adjuvants is challenging, and adjuvants are under regulatory scrutiny as a result of theoretical and reported safety concerns [1], which include the risk of developing autoimmune diseases or AID, even if these concerns are controversial due to confounding factors that may attribute to the onset of AID. While research is constantly evolving to enhance adjuvant design [2], the scope of this manuscript focuses on two types of adjuvants in marketed vaccines: oil-in-water emulsions (e.g., squalene-based emulsions being used in influenza vaccines) and toll-like receptor (TRL) agonists (e.g., monophosphoryl lipid A (MPL)/aluminum salt combination in Hepatitis B and human papilloma virus (HPV) vaccines).

Possible safety concerns have arisen from studies in which adjuvants have induced AID in various animal models and from reports (primarily from one laboratory) that diverse compounds with "adjuvant" activity could be associated with silicosis, Gulf war syndrome (GWS), macrophagic myofasciitis (MMF), and post-vaccination phenomena [3]. The recent cases of narcolepsy observed during the 2009 pandemic influenza campaign with an AS03-adjuvanted vaccine [4,5] have further heightened awareness.

Autoimmunity and AID are complex and result from a combination of genetic, hormonal and/or environmental triggers [6]; thus, attributing causality is not easy. Certain adjuvants have specific receptor targets that strongly stimulate the immune system via pattern recognition receptors (PRRs), including TLRs, and stimulating

Abbreviations: AID, autoimmune disorders; AF, adjuvant formulations; ASIA, autoimmune/inflammatory syndrome induced by adjuvants; CFA, complete Freund's adjuvant; CIA, collagen-induced arthritis; DA, dark Agouti; DC, dendritic cells; EAE, experimental autoimmune encephalitis; EMA, European Medicines Agency; GWS, Gulf war syndrome; HESI, Health and Environmental Sciences Institute; HLA, human leukocyte antigen; HPV, human papilloma virus; Hsp, heat shock protein; IBD, inflammatory bowel disease; IFA, incomplete Freund's adjuvant; IFN, interferon; IL, interleukin; ILSI, International Life Sciences Institute; IMI, Innovative Medicines Initiative; MG, myasthenia gravis; miRNA, micro-ribonucleic acid; MMF, macrophagic myofasciitis; MoA, mechanism of action; MPL, monophosphoryl lipid A; mRNA, messenger ribonucleic acid; MS, multiple sclerosis; NOD, non-obese diabetic; O/W, oil-in-water; PAMPs, pathogen associated molecular patterns; PRRs, pattern recognition receptors; PY, person years; RA, rheumatoid arthritis; SjS, Sjögren's syndrome; SLE, systemic lupus erythematosus; snRNPs, small nuclear ribonucleic particles; TLRs, toll-like receptors; Tregs, regulatory T cells; UTR, untranslated region; W/O, water-in-oil; WOW, water-in-oil-in-water.

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such targets could theoretically increase the risk of initiation or progression of systemic AID [7].

As a consequence, questions are raised that need to be considered, such as: is the induction of AID in experimental settings due to exaggerated immune activation through the use of adjuvants? What is the relevance of animal data to humans? Do adjuvants induce autoimmunity and/or AID as a result of an exaggerated effect in a clinical setting, i.e., can some autoimmune diseases inherently be associated with adjuvants?

To address these questions, the International Life Sciences Institute (ILSI) Health and Environmental Sciences Institute (HESI) formed a multi-sector, international scientific committee, the Vaccines and Adjuvants Safety Project Committee (HESI committee), in 2011 to conduct a multi-faceted approach to assess the state of the science on adjuvants and AID. This approach included a survey of the current experimental and epidemiological literature and the convening of a Workshop on Adjuvants and Vaccines: Focus on Autoimmunity on October 18–19, 2012 in Amsterdam, The Netherlands. The workshop brought together 35 international scientists from academia, industry, and government to deliberate the relationship between adjuvants and vaccine safety [8].

2. Interplay between vaccines and the immune system is a delicate balance

The immune system is designed to recognize dangerous vs. safe antigens. It is a delicate system with many components that involve cells and signals that "turn on" and those that are responsible for "turning off" a response once the insult has cleared. Vaccines, and with the help of adjuvants, are designed to utilize this delicate balance in the immune system to drive protection for a host from viral, bacterial, or fungal infection. The physical–chemical properties of adjuvants and how they interact with the antigen(s), are important in defining how the immune system may respond, albeit to promote a protective humoral response or a response biased toward cell-mediated immunity. Antigen selection and adjuvant design are no longer empirical, and new generation adjuvants can specifically direct the desired immune responses [9]. Adjuvants, like oil-in-water or TLR agonists are designed to promote a more robust and/or tuned immune response to the antigen in the vaccine formulation in order to provide better protection. Oil-based emulsion adjuvants include MF59 (squalene), ASO3 (squalene, α-tocopherol), and Montanide (Seppic; various metabolizable and mineral oils). There are abundant animal study data on one example of this class of adjuvants, MF59 [10]. These data illustrate the complex molecular mechanisms associated with this class of adjuvants as illustrated in Fig. 1. MF59 both increases the uptake of antigens by antigen presenting cells (e.g., dendritic cells) and activates the innate immune response locally, providing the critical immunologically competent micro-environment for productive generation of B and T cell immunity. Importantly, MF59 does not activate the immune system systemically, and does not lead to detectable polyclonal immune activation even in the draining lymph node. Thus, a critical aspect of safe and highly effective adjuvants is one that can act locally at the site of injection in order to limit systemic effects, and therefore enhance its probability to be safe while still in an active form from an immune perspective.

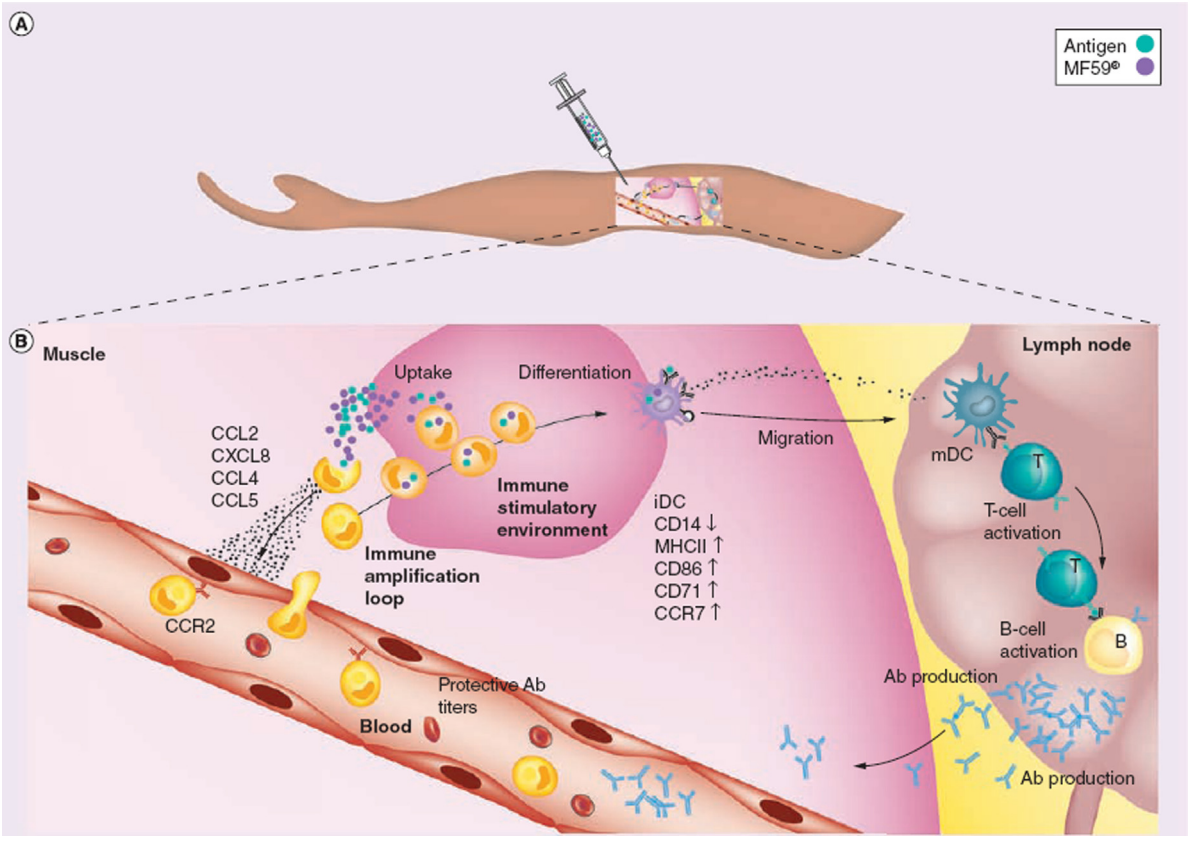

Fig. 1. Current understanding of MF59® adjuvant activity. (A) MF59 adjuvant in combination with a vaccine antigen is injected into the muscle. (B) In the muscle, tissue-resident monocytes, macrophages, and dendritic cells are activated and respond by inducing a mixture of chemokines (CCL2, CXCL8, CCL4, and CCL5), which results in a significant influx of phagocytic cells that take up the antigen and differentiate into antigen-presenting cells (dendritic cells). These cells are responsible for the efficient transport of antigen to the lymph nodes, where the immune response is triggered through the activation of T and B cells and antibody production. Ab: Antibody; iDC: Immature dendritic cell; mDC: Monocytic dendritic cell. Reprinted from Vaccine, 30, O'Hagan DT, Ott GS, De Gregorio E,and Seubert A. The mechanism of action of MF59–an innately attractive adjuvant formulation, 4341-8, copyright (2012), with permission from Elsevier [10].

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