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Vaccine and Adjuvant Mediated Autoimmunity

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Author's contribution

The sole author designed, analyzed, interpreted and prepared the manuscript.

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Opinion Article

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ABSTRACT

The macrophage, natural killer cells, B and T cells are the outstanding formed elements of human immune system. In normal immune homeostatic state these cells in a way or other recognize the host body components as self via the immune surveillance mechanisms. Though when there was a shift in immune homeostasis due to chronic induction by; i - environmental stimulus, ii –interplay of predisposing genetic elements, iii-family history, iv – bystander pathologic inflammatory system .Immune cells becomes prone to recognize the impart self or self as a non-self with subsequent induction of autoimmune diseases. The present opinion paper was aimed at vaccine and adjuvant mediated autoimmune diseases. Timelines for vaccine and adjuvant induced autoimmunity were made. Different human approved vaccines induce different autoimmune disease, more than on vaccine may induce same autoimmune disease. Shoenfeld Syndrome, the adjuvant induce autoimmune/ inflammatory syndrome. Under the umbrella of this syndrome five conditions grouped as; i – Postvaccination with an adjuvanated vaccine, ii – macrophagic myofasciitis, iii – sick building disease condition iv – Gulf war disease condition and v – siliconosis. Protocol for the practical evaluation of these diseases was suggested. Understanding Shoenfeld Syndrome is crucial for producing vaccines with a safer side effect profile.

Keywords: Adjuvant; autoimmunity; cell; component; disease; immune; inflammatory; vaccine.

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1. INTRODUCTION

Vaccines and adjuvants are impactful onto human health welfare. Since vaccine is currently holding a dual immune functions. First, preventive and second therapeutic [1,2]. Though Vaccine may induce rather un-beneficial adverse effects. Such un-beneficial effects are known as vaccine associate disease enhancement and vaccine failure. Among these vaccine associate disease enhancement are the evolution of auto antibody and autoreactive cells to self human body components with expression of clinical disease, the autoimmune diseases [3,4]. The objective of the present opinion paper was present an at glance insight to vaccine and adjuvant mediated autoimmunity.

2. INFECTION

In an environmental ecologic niche and/or human body microecologic niche, there were sources of microbes with a hidden pathogenic potentials. When these niches realeases their harbored potential pathogens through a transmission cycle to human body [environment niche] or released to migrate to other organs within the human host body[micro-niche].The potential pathogen find port of entry, gain foot hold and propagated in certain predilection sites whereby producing virulence factors and Qouram sensing factors empowering them to overwelme the host producing disease. These events are collectively known as infection [5].

3. VACCINES

Vaccine is the non-pathogenic version of a pathogen or its molecular subunits, separated, purifid and standarised. Such preparation found to be; pure, safe, immunogenic and immune effective. The action spectra of vaccine includes preventive and therapeutic effects [1,2,6].

4. ADJUVANT

In the immune sense, adjuvant is that preparation(s) that can highthen the immune response to an immunogen in term of concentration, intensity and/or titre as compared to that without the adjuvant. Adjuvants are either used pre-immunization for conditioning or mixed directly with the immunogen or applied after priming with the immunogen. Adjuvants are helpful for haptens and moleculare immunogens. The action mechanisms of adjuvants are; antigen targeting,cytokine network, and or epitope spreading. The chemical composition of adjuvants found to be markedly heterogeneic. They may enhance, TH2, TH1 or both TH1&TH2 cell responses [7,8].

5. IMMUNE SYSTEM

Human genome consists of genetic system and gene sets that encodes the immune and non-immune physiologic functions of the immune system. Immune system can be subdivided in to systemic and mucosal immune system. The systemic immune system got number of components as; Genetic component, hemopoietic component, lymphoid component, complement and kinin component. While the mucosal immune system composed of number of mucosal associated lymphoid compartments in structural sense. In functional sense it is composed of inductive and effector sites [9,10].

6. IMMUNE RESPONSES

When the immune system face an external or internal insults [antigens, allegens, haptens], the immune response to these immunogens can be; humoral, cellular, both humoral and cellular. The in practice functional importance of the immune responses are either for protection or diagnostic values. The nature of the immune responses to different immunogens are innate, immune cross-roads and adaptive responses. Natural or innate responses instruct for initiation of adaptive responses; immune cross roads expressed as cells or mediators that can performed both innate and adaptive immune functions. The immune response time curve includes primary and secondary immune responses. The immune cell events takining part in the immune responses may ramify the immune responses to;

i. Humoral, cellular, both humoral and cellular response

ii. allergenic responses

iii. toleragenic responses

iv. anergic responses

v. Autoimmune response [10].

7. AUTOIMMUNITY, A CLASSICAL VIEW

When the effector immune cells starts to respond to the molecular component of self tissues and

self cells and produce pathologic effects this is known as autoimmunity. The autoimmune responses can be normal physiologic responses termed as physiologic autoimmunity expressed as the baseline antibody and/or autoreactive cell levels. Or it can be pathologic autoimmunity which lead at most to an immune tissue injuries ultimated by onset of autoimmune disease. Autoimmunity may happend as post infection or post vaccination as a chronic course sequalae [11,12].

8. AUTOIMMUNITY; CURRENT MOSAIC THEME

The mosaic theme can be formulated as the novel factors of autoimmunity that are of multifactorial origin and diversity of expression autoimmune disease in man. The term covers different combination of factors that are involved in autoimmunity and produce varying and unique clinical presentation in a wide spectrum of autoimmune disease. Four categories of factores involved in autoimmunity as; Genetic, hormonal, immune difficiency and envirnmental factors. The environmental factors includes; infectious agents, vaccines, adjuvants and smoking [12]. Three main molecular mechanisms valid for explaining autoimmunity as; Tolerance, molecular mimicry, and epitope spreading. Tolerance can be established through clonal deletion, anergy, clonal ignorance and regulatiry T cell function [13].

9. ANALISING AUTOIMMUNE DISEASE

Autoimmunity is outstandingly considered to be a result of interplay between genetic predisposition and environmental factors. Such interplay have been described as heterogenic and complex. The heritability of these diseases has been well documented and quantified [14], and exhibit three important features; (i). all genetic disease have strong genetic components, (ii). relatively large numbers of risk alleles are shared between multiple autoimmune diseases, (iii). the product of most of the autoimmune associated genes are parts of immunological pathways in particular T cell signaling, TNF signaling or innate immunity [15]. These features indicate that the onset of great majority of cases of autoimmune disease occure in adulthood, and suggested that these conditions are results of pathological responses mounted by the immune system as a reaction to environmental stimulii. The analysis of the autoimmune disease reaveals a stepwise sequence of four rules that starts with: (i). foundation of predisposing genetic arcitecture representing autoimmunity, (ii). chronic reapeated skewed and baised responses over years yield pathological system (iii). the pathological system induces loss of immune tolerance and (iv). aquire notious potentials. Based upon these four rules of the conceptual landscape leads to four endivors that will improve the understanding of autoimmune diseases. These endevors were as follows;

(i). How do genetic variants define the immune system behavior before and after the onset of the autoimmunity.

(ii). How does the immune adaptation facilitate the develoment and perpetuation of autoimmne diseases.

(iii). Which genetic element trigger pathological immune behavior.

(iv). How do local tissue factors modulate the function and survival of infiltrating immune cells [11].

10. VACCINE AND ADJUVANT INDUCED AUTOIMMUNE DISEASE

Vaccine induced autoimmunity timle line was presented in Table 1. From 2012 untill 2022 a spectrum of human autoimmune diseases have been reported following vaccination, Table 2. The molecular mechanisms operating in autimmunity induction by vaccines are identified as; molecular mimicry, bystander activation and immune cross-reactions [15,16,17,18]. The adjuvant induced autoimmunity timelins was presented in Table 3. Adjuvants are able to initiate autoimmunity via avaiety of mechanisms like; Alteration of host immune system, polyclonal activation of B cells ,viral induced antibodies and acceleration of molecular mimicry [18,19,20]. Five conditions include under the umbrella of Shoenfeld syndrome the, Autoimmune/ inflammatory syndrome induced by adjuvants as i – Post vaccination with adjuvanate vaccine ii – macrophagic myofaciitis, iii – sick building condition iv - Gulf war condition and v – siliconosis [19].

Table. 1. Vaccine associated autoimmune disease Timline

Acheivment	Date	Reference
Vaccine-autoimmunity relationship still obscure	1996	[21]
Vaccine-autoimmune disease notion is contraversial	2000	[22]
Aquired autoimmunity post to viral vaccination	2008	[23]
Vaccine induced GBS, thrembocytopenia purpura, myocarditis	2010	[24]
Mechanisms operating in vaccine induced autoimmunity; molecular mimicry, immune cross-reaction	2018	[16]
Molecular mehanisms of vaccine-autoimmunity are; molecular mimicry bystander activation and cross-reactivity	2023	[17]

Table 2. Examples of Vaccine induced autoimmune diseases

Inducer vaccine	Disease type	Reference
HBV	Neuropsycatric disease	[25]
Infleunza	Endocrine autoimmune disease GBS	[26] [27]
HPV	Gastroentritis, SLE, CNS, arthritis	[28]
Sars-cov-2	GBS, myocarditis, thermbocytopenia purpura	[29-31]

Table 3. Adjuvant induced autoimmune disease timeline

Acheivment	Date	Reference
Klebsiella pneumoniae capsular polysaacharide and tissue extract produce lesion	1977	[32]
Oil containing microbial adjuvant induce autoimmune arthritis	1980	[33]
CpG oligoneucleotides are potent adjuvant for activation of encephallitogenic T cells	2000	[34]
Hydrocarbon oil,squalene induce lupus autoantibody in mice	2003	[35]
Squalene induce autoimmunity	2004	[36]
Squalene,aluminium hydroxide miniral oil,Iodin gadital are inducing adjuvant autoimmunity	2014	[37]
Adjuvant induced autoimmune/inflammatory syndrome[Shoenfeld syndrome,ASIA] and thyroid autoimmnity	2016	[19,20]
Major and minor criteria for diagnosis of ASIA were formulated	2023	[18]

11. SHOENFELD SYNDROME

This syndrome stands as molecular immunogenetic phenomena with chrarcteristic autoimmune reactions noticed post to adjuvant application in some human beings. Shoenfeld and his colleagues[19] have been coining its specific entity (Autoimmune/ Inflammatory Syndrome Induced by adjuvant ISIA) as Shoenfeld Syndrome. As the adjuvant vary the nominaion of the disease varied. But there were a common pathway for the autoimmune pathogenesis. So, there were five sub-entities ensembled under the umbrella of this syndrome as; Postvaccination with adjuvanated vaccine, macrophagic myofasciitis, sick building illness, Gulf war illness and siliconosis. The adjuvant nature can be; Alum, polypropylene mesh, silicon, squalene and infectious agent intrinsic adjuvant. Chronic stimulation by any of these adjuvants in addition to the presence of genetic predisposition with strong sharing genetic elements, sharing immune pathway together with the interplay of pathogenic allele leading to initiation of autoimmune pathology system. This mechanism times my need promotion by specific HLA haplotype to finalize the mechanism of induction of the onset of the autoimmune disease. The forementioned sub-entities shared almost same clinical manifestion. Removal of the adjuvant from the in question patients improve the state of the patient [39,40].

12. VIRAL HEPATITIS VS SHOENFELD SYNDROME

In 2003, one of my Ph.D. students [41] had been investigating the prevalence of an array of autoantibodies in chronic hepatitis B & C patients as apart of her Ph.D project, she had been found that hepatitis B & C patients showed higher levels of autoantibodies than controls.18% of the patients have at least on type of the test auto-antibodies. Rheumatoid factor showed 14/104 ,13.46%. While, antinuclear factor auto-antibodies were 5/104,4.81%. Apprantly, hepatitis virus may either have sharing antigenic epitope and/or bear sort of intrinsic adjuvaninicty promoting auto immune reactions and antibody production in which they were in line with basic steps of Shoenfeld Syndrome [39,40].

13. DIAGNOSIS

Vaccine and adjuvant induced autoimmune disease can be diagnosed through the use of Seida et al [18] in which four major and four minor criteria were typically eligible for diagnosis, they recommend even the fullfilment of two major or one major and two minor criteria are sufficient for diagnosis. The major criteria were; (i). exposure to external stimuli, (ii). appearance of typical clinical manifetation, (iii). biopsy reveal typical histologic findings (iv). dysautonomia and (v). removal of external stimuli improve the symptoms while the minor criteria were including; (i). appearance of adjuvant specific auto-antibody, (ii). appearance of secondary clinical manifestation, (iii) evaluation of clinical autoimmune disease, and (iv). disease linked to specific HLA antigen [18]. From the fore going paragraphs [1-41], an eight points protocol was suggested for evaluation of of vaccine and adjuvant induced autoimmue disease as;

1. The in question vaccine and adjuvant are approved for human use in vaccination programs.

2. Patient has been subjected to repeated shuts of the vaccine or adjuvant through long time period

3. The disease onset happened following vaccine or adjuvant application.

4. Pathologic Inflammatory system got evaluated.

5. Mapping the predisposing genetic elements.

6. Vaccine could produce an analogus disease in laboratory animal model with similar immune tissue injury to that of man.

7. Patients autoantibody and/or autoreactive lymphocyte when transfered to lab animal could produce the disease.

8. Discontinuation of the course of Vaccine or adjuvant application improve the wellbeing both in man and laboratory animal [38].

14. CONCLUSION

Vaccine and Adjuvant induced autoimmune diseases were rare but are documented in the current literature. Timelines for vaccine and adjuvant induced autoimmunity were presented. Mechanistic analysis of autoimmune disease and Shoenfeld syndrome were briefed. The objective

behind the presentation of this opinion paper was to bring attention to; (i). importance of undrstanding the risk factors and mechanisms of shoenfeld syndrome for diagnosis of suspect cases of post vaccine and adjuvant application (ii). A suggestion of an eight points protocol for evaluation of Vaccine and adjuvant induced autoimmune disease, and (iii). understanding the theme of Shoenfeld syndrome is crucial for developing vaccines with safer side effect profiles.

CONSENT AND ETHICAL APPROVAL

It's not applicable.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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