International Immunopharmacology 19 (2014) 17–26

Contents lists available at ScienceDirect

International Immunopharmacology

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

Review

Are the anatomical sites for vaccine administration selected judiciously?

Basant Malik, Goutam Rath, Amit K. Goyal *

Department of Pharmaceutics, ISF College of Pharmacy, Moga, Punjab, India
Punjab Technical University, Kapurthala, Punjab, India

ARTICLE INFO

Article history:
Received 27 August 2013
Received in revised form 18 December 2013
Accepted 22 December 2013
Available online 7 January 2014

Keywords:
Anatomical site
Vaccine
Dendritic cell
Topical vaccine
Antigen presentation

ABSTRACT

Route of vaccine administration plays an important role in the development of immune response. Antigen administered via different anatomical sites interacts with diverse subsets of antigen presenting cells. Diverse population of antigen presenting cells directs a drastically different immune response. Initially, the recommended routes for vaccine administration were also selected on the basis of clinical trials conducted for the drug molecules. However, physicochemical and pharmaceutical behaviors of proteins (antigens) and chemical compounds are entirely different. Most of the commercial vaccines are injected in the arm or in the scapular region (deltoid muscle). Vaccine administered to these conventional anatomical sites has failed to induce desired immune response due to lack of optimum level of antigen presenting cells. In this review, we have discussed the importance of the selection of anatomical sites for vaccine administration. Mere selection of an optimum site for vaccine administration may drastically change the immune response of the current marketed formulations without any alteration in their existing production plans.

Contents

* Corresponding author at: ISF College of Pharmacy, G.T. Road, Ghal Kalan, Moga 142001, Punjab, India. Tel.: +91 98782 86888; fax: +91 1636 236564.
E-mail address: amitkumargoyal1979@gmail.com (A.K. Goyal).

1567-5769/$ – see front matter
http://dx.doi.org/10.1016/j.intimp.2013.12.023

1. Introduction

Vaccination is the only way to eradicate highly infectious diseases. In the past few years, massive efforts have been made to improve the effectiveness of the existing vaccines. Development of novel nanocarriers for effective vaccine delivery has become a thrust area of research [1–3]. Several attempts have been made for the selection of optimum routes for vaccine administration in order to induce strong immune response [4–6]. Despite huge investment and massive trials we are unable to achieve this milestone till date. In the past few years attempts have been made for targeted vaccine delivery to specific immune cells viz. microfold cells [2,7,8], dendritic cells [9,10] and macrophages [11,12]. Current marketed vaccines are administered through conventional routes including muscles and the subcutaneous layers which possess a limited population of the dendritic cells (DCs) [13]. It is a well accepted fact that vaccination via different anatomical sites results in significantly altered immune response. It may be attributed to the differential lymphatic transport of the antigen administered via different anatomical sites in the body [14,15]. Guy and coworkers studied the effects of the adjuvant and site of parenteral immunization on the serum and mucosal immune responses. Priming in the back resulted in the increased mucosal IgA and IgG1 and decreased local IgG2a responses compared to neck priming [16].

Various parameters such as route of antigen delivery, delivery vehicle, dose, injection site, technique and adjuvant can alter the immune response [16–18]. These parameters can alter not only the effective dose of the antigen reaching to the antigen presenting cells but also the subpopulation of the dendritic cells involved in presentation [19]. de Lalla and coworkers conducted an excellent case study using two hundred ninety nine human volunteers to study the relationship between anatomical sites for vaccine administration and immune response [18]. The highest rate of seroconversion was found in subjects immunized via intramuscular route into the deltoid muscles as compared to the gluteal (I.M.) and subcutaneous administration. Shaw and coworkers have also reported the significance of the selection of suitable anatomical site for vaccine administration. They administered vaccine into the arm and in the superficial and deeper layers of the buttocks. On comparing these anatomical sites, they concluded that maximum antibody titer was induced in the case of group vaccinated through the arms. Vaccines administered via superficial layers of the buttocks resulted in the induction of poor immune response [20].

Dendritic cells (DCs) play an important role in the development of pathogen specific T and B cells [21]. Interestingly, DCs are region specific and are appointed by the nature to the specific location for precise functions depending upon their exposure to an external environment. The mesenteric lymph nodes (mLN) and the axillary lymph nodes (axLN) possess entirely different subsets of DCs and behave differently even against identical pathogen. Similarly, spleen and thymus also possess completely different subsets of DCs [22]. Previous studies revealed that the location of the DCs not only affects the nature and extent of immune response (helper or cytotoxic) but also defines the in-vivo fate of the DCs.

The nature of DC involved in the antigen presentation controls the expression of tissue-specific homing receptor of T cells and thus controls their trafficking throughout the body. The DCs in the axLN are identical to MHCIIhi CD103 cells, which are exclusively present in the skin (Langerhans cells) [23] while, mLN possess entirely different subsets of dendritic cells (MHCII+ CD103+) and are identical to the DCs present in the lamina propria of the gut [24]. Surprisingly, upon transplantation of axLN into the drainage area of the mLN the DC subset composition of the axLN gets converted to that of the mLN. Therefore, the microenvironment at different anatomical sites controls the phenotypes of the DC. The axLN and mLN DCs play a different role in the immunity. Some studies showed that these different DC subsets possess different affinities for Mycoplasma arthritidis mitogen (MAM) binding, which indicates the difference in their capacity to stimulate T-cells. The mLN-specific DC mainly secretes Th2 cytokines (e.g. IL-4) which are favorable for the development of B cell mediated immune response. However, the axLN specific DC produces Th1 cytokines (IL-12) to activate the macrophages. Moreover, in the axLN major populations of DCs were CD4+ and SIRP+. These are primarily involved in the activation of T cell dependent immune response. Interestingly, it was also found that axLN DCs also express the NKR-P1A receptor. DCs with NKR-P1A receptor were found to exhibit a strong catalytic activity [25]. In contrast, in the mLN only about 50% of the region-specific DCs were CD4+ and SIRP+ [26]. Therefore, axLN and mLN dendritic cells have a different role in immunity. Similarly, different subsets of DCs are playing different roles at different anatomical sites of the body. It was found that antigen administered in the different layers of the skin generates entirely different immune responses. Recently, Banchereau et al. reported that human epidermal Langerhans cells (LCs) are more efficient than dermal CD14(+) DCs for the activation of potent cytotoxic T lymphocytes (CTLs). These distinctive dendritic cells (DCs) express different cytokines (IL-15 produced by LCs and IL-10 expressed by dermal CD14(+) DCs) [27]. Similarly, in the lungs the uptake, transport, and presentation of antigen by lung dendritic cells (DCs) also play a dominant role in the initiation of CD8 T cell responses. The CD11b(low/neg)CD103(+) DCs play a critical role in the activation of cytotoxic T cell responses. Ho et al. demonstrated that CD11b(low/neg)CD103(+) DCs are the dominant lung DC population involved in the transport of influenza virus to the posterior mediastinal lymph node. However, CD11b(high) CD103(neg) DCs are more efficient for taking up the virus within the lung and these rarely migrate to the lymph node and reside in the lung to produce pro-inflammatory cytokines. Moreover, the CD11b(low/neg)CD103(+) DCs present the antigen via MHC class I complexes and potently induce CD8 T cell proliferation. These findings proved the central functioning of CD11b(low/neg)CD103(+) DCs for the transport of antigen (Ag) from the lung to the lymph node and also for efficient processing and presentation of viral Ags to CD8 T cells [28].

In such a situation where the type and extent of immune response change drastically with a slight change in the site of vaccine administration, how can we even think to administer each vaccine in the same manner? Now on the basis of these findings we can strongly recommend that we should select optimum anatomical site for vaccine administration to achieve desired immune response. We should set our priorities (humoral or cellular response) before selecting the anatomical site for vaccine administration.

2. Induction of immune response

The induction of immune response starts with the activation of dendritic cells of peripheral lymphatic network, where the invading organisms are broken down. The dendritic cells then warrant the lymphocytes about the invading organism which leads to the differentiation and proliferation of lymphocytes in lymph nodes. Afterwards, the mature lymphocytes migrate to the desired sites for necessary action. Research findings reveal that besides DCs, monocytes [29], macrophages, neutrophils [30], and B-lymphocytes [29] also participate in antigen presentation. However, antigen presentation by these different APCs will be different and the immune response also may vary significantly [31]. These results have led to new vaccination strategies based on novel nano-carriers for targeted antigen delivery to specific APCs to improve the immune response [24].

Studies have been conducted to correlate the physical and chemical processes that can alter the immune response. Even in the presence of highly sophisticated techniques our understanding of the lymphatic system seems to be incomplete. This scarcity may be imparting hindrances in development of a highly efficient vaccine or we are not utilizing the available information in a justified way. It should be noted that the physical and chemical interactions between the components of immune system during the bio-fate of the antigen are also of great