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Short communication

A preliminary study of chemo- and cytokine responses in rabies vaccine recipients of intradermal and intramuscular regimens

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ABSTRACT

Plasma from 10 patients who had received rabies vaccine either intradermally (ID) or intramuscularly (IM) was examined for 20 chemo- and cytokines. Plasma samples were withdrawn on days 0, 3 and 7 after vaccination. These chemo- and cytokines and sampling days were chosen based on data collected from a protein array analysis of 122 cytokines conducted on one recipient of vaccine administered IM and one recipient of vaccine administered ID. Although eotaxin, interleukin (IL)-5 in the ID and IL-1 beta in the IM group were the only chemo- and cytokines that reached statistical significance ($p < 0.05$), the overall trends may suggest bias on Th1 or Th2 according to vaccination routes. IL-1 alpha, -2, and -6, hemofiltrate cysteine–cysteine chemokine (HCC-4), glucocorticoid induced tumor necrosis factor receptor (GITR), tumor necrosis factor (TNF) related apoptosis inducing ligand-receptor (TRAIL-R3) had some degree of elevation in the ID group. TNF-alpha, gamma-interferon, granulocytes/macrophages – colony stimulating factor (GM-CSF), transforming growth factor (TGF)-beta, lymphotactin and pulmonary and activation-regulated chemokine (PARC) were elevated, although not to a significant level, in the IM group. IL-12, interferon-inducible T cell alpha chemoattractrant (I-TAC) and sertoli cell factor (SCF) were not significantly elevated in both groups whereas IL-4 and -10 were unchanged. Further studies are required to determine whether the presence of specific chemokines, such as eotaxin, is responsible for the production of high levels of rabies virus neutralizing antibody after administration of the dose-sparing ID regimen.

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1. Introduction

The intradermal (ID) route for rabies post-exposure prophylaxis (PEP) was introduced in 1985 in Thailand [1]. By 1988, ID regimens for PEP completely replaced the use of 14–21 subcutaneous injections of the nervous tissue derived vaccine produced in sheep (Semple) and suckling mouse brain (Fuenzalida) vaccines in Thailand. These nervous tissue derived rabies vaccines induced an unacceptable rate of neurological complications and were of unreliable immunogenicity [2–4]. The World Health Organization (WHO) subsequently endorsed and approved the use of ID for PEP in 1992 [5]. Since the introduction of the economical ID PEP strategy, rabies deaths in Thailand have declined from 185 (in 1990) to 68 (in 1999) and 19 (in 2004) [6]. In 2009, 24 deaths were reported (data of ministry of public health, Thailand, unpublished).

The most widely used ID regimen for rabies PEP is the Thai Red Cross (TRC) regimen. The TRC regimen consists of injecting 0.1 ml of WHO approved tissue culture rabies vaccine intradermally at two different lymphatic drainage sites on the left and right upper arm on days 0, 3, 7 and 28 [7]. The amount of vaccine required for PEP can be significantly reduced when the TRC ID regimen is used. For example, the Essen IM PEP regimen requires 5 vials (one vial is administered on each of days 0, 3, 7, 14, 28) whereas the TRC ID regimen requires only 1 or 2 vials, depending upon the volume of the IM dose of rabies vaccine [0.5 and 1.0 ml preparation of purified Vero cell and purified chick embryo vaccine (PCECV) respectively]. The immunogenicity and efficacy of the TRC ID regimen have been proven in several clinical trials [8–10]. The long term antibody persistence and confirmation of an anamnestic response after vaccination with a tissue culture rabies vaccine have also been confirmed for both IM and ID vaccination. In one study, conducted in Vietnam, patients vaccinated 5 years previously responded with an anamnestic response to one booster dose of vaccine [11]. Long lasting immunity was also confirmed in a clinical trial conducted in 118 Thai patients that received pre-exposure vaccination (PreP)

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or PEP with a tissue culture vaccine administered by either the ID or IM route 5–21 years previously and subsequently were boosted with 2 ID doses of vaccine [12].

ID vaccination is a method of delivering antigen into the dermis via syringe and needle [13]. ID administration of vaccine has several advantages including the fact that less antigen is required, thus sparing vaccine, and it also allows antigen to be delivered directly to the skin where it can come into immediate contact with resident hematopoietic-derived cells [including mast cells, antigen presenting dermal dendritic cells (DC), macrophages], thus initiating an excellent immune response. Epidermal Langerhans' cells are also present in the papillary dermis. Additionally, extravasation of leucocytes and DC precursors from the blood are produced in the dermis. The humoral immune response to rabies vaccination administered either ID or IM, are comparable [13]. Published data indicate that an anamnestic response occurs in patients previously vaccinated by either the IM or ID regimen and subsequently boosted by either the ID or IM route [14].

Despite sizable reports on immunogenicity, efficacy and safety of the ID route of rabies vaccination, many physicians in rabies endemic countries remain doubtful and question how ID works by using only a small proportion of the IM dose. This led to underutilization of ID rabies vaccination in many Asian countries where WHO approved tissue culture rabies vaccines are not affordable and there are still high rabies deaths. Earlier studies focused on rabies antibody response but in this enclosed study, we examined the effect that the route of administration of rabies vaccination (IM or ID) had on the production of chemo- and cytokines in patients that received PEP. The results of our study suggest that there may be differences in Th responses between patients that are vaccinated by the ID route vs. those vaccinated by the IM route and that certain chemokine may play a role after vaccination using the ID regimen.

2. Materials and methods

2.1. Subjects and informed consent

The protocol of the study was reviewed and approved by the Ethics committee, Queen Saovabha Memorial Institute, Thai Red Cross Society. The design was cross-sectional. The subjects were consecutively selected according to the inclusion/exclusion criteria and were randomly allocated to the IM or ID group. The inclusion criteria were healthy individuals whose ages were between 18 and 25 years. There was no past history of or feature suggesting diseases which might affect the immunological systems. They had category II rabies exposure according to WHO criteria which required vaccination without rabies immune globulin. All of them were thoroughly explained before they signed an informed consent. The informed consent was collected from each subject enrolled in the study. Any individual with age below 20 years old also had his/her parent co-signed the informed consent. Exclusion criteria included those who were not healthy or had underlying medical diseases and who received rabies vaccination in the past.

2.2. Study design and setting

Initially, a screening group consisting of two subjects was immunized with either an ID or IM regimen of rabies PEP using PCECV (Chiron Behring; Lot no. L1032; potency, 10.23 IU/dose). Serum was collected on days 0, 3, 4 and 7 after primary immunization was initiated. Following an analysis of the data collected from the 2 initial subjects selected for the screening group, 20 subjects, 10 in each group, were immunized with either ID or IM rabies PEP regimen using PCECV. Blood samples were collected from all subjects on days 0, 3 and 7.

Table 1
List of cytokines and chemokines and their functions that were examined in this study.

	Functions
IL-1 alpha,beta	Upregulated adhesion molecule expression, neutrophil and macrophage emigration.
IL-2	T cell activation and proliferation, B cell growth, NK cell proliferation and activation, enhance monocyte/macrophage cytolytic activity.
IL-4	Stimulates T_H2 helper T cell differentiation and proliferation. Stimulates B cell Ig class switch to IgG1 and IgE anti-inflammatory action on T cells, monocytes.
IL-5	Regulates eosinophil migration and activation.
IL-6	Induction of T and B cell differentiation and growth.
IL-10	Inhibits macrophage pro-inflammatory cytokine production, down-regulates cytokine class II antigen and B7-1 and B7-2 expression, inhibits differentiation of T_H1 helper T cells, inhibits NK cell function, stimulates mast cell proliferation and function, B cell activation and differentiation.
IL-12	Induces T_H1 T helper cell formation and lymphokine-activated killer cell formation. Increases CD8 + CTL cytolytic activity; decreases IL-17, increases IFN-gamma.
IFN-gamma	Regulates macrophage and NK cell activations. Stimulates immunoglobulin secretion by B cells. Induction of class II histocompatibility antigens. T_H1 T cell differentiation.
TGF-beta	Down-regulates T cell, macrophage and granulocyte responses. Stimulates synthesis of matrix proteins. Stimulates angiogenesis.
TNF-alpha	Fever, enhanced leukocyte cytotoxicity and enhanced NK cell function, pro-inflammatory cytokine induction.
Eotaxin	Chemoattractant for eosinophils and basophils. Acts in concert with IL-5 to activate eosinophils.
Lymphotactin	XCL1, member of the XC chemokine family affecting T cell and natural killer cell.
PARC	Belongs to CC-chemokine. PARC is chemotactic for both activated CD3 T cells and non-activated CD14 lymphocytes but not for monocytes and granulocytes.
SCF	Stimulates hematopoietic progenitor cell growth, mast cell growth.
GITR	GITR is involved in the regulation of T cell receptor mediated cell death (resistance to apoptosis).
GM-CSF	Mediator of dendritic cell maturation and function. Regulates myelopoiesis.
HCC-4	Ligand of CCR5 chemokine family affecting T cells and monocytes.
I-TAC	CXCL11 chemokine ligand of CXCR3. A chemokine receptor on type 1 helper cells, mast cells and mesangial cells.
TRAIL-R3	TRAIL receptor-3 is not capable of inducing apoptosis. TRAIL receptor-3 can compete for TRAIL. It is capable of inhibiting apoptosis mediated by TRAIL and serves as a decoy.

IL, interleukin; IFN, interferon; NK, natural killer; TGF, transforming growth factor; TNF, tumor necrosis factor; PARC, pulmonary and activation-regulated chemokine; SCF, sertoli cell factor; GITR, glucocorticoid induced tumor necrosis factor receptor; GITR, glucocorticoid induced tumor necrosis factor receptor; GM-CSF, granulocytes/macrophage – colony stimulating factor; HCC, hemofiltrate cysteine–cysteine chemokine; I-TAC, interferon-inducible-Tcell alpha chemoattractrant; TRAIL-R3, TNF related apoptosis inducing ligand-receptor.

2.3. Evaluation of serum samples

Serum was separated from blood samples collected from all subjects and was analyzed for the presence of rabies virus neutralizing antibody (RVNA) by the Rapid Fluorescence Focus Inhibition Test

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