ORIGINAL REPORT

Antibody Responses to Trivalent Influenza Vaccine in Iranian Adults Infected with Human Immunodeficiency Virus

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Received: 5 Mar. 2012; Received in revised form: 18 Nov. 2012; Accepted: 4 Jan. 2013

Abstract- The serious influenza-associated complications among immunodeficient individuals such as those who are infected with human immunodeficiency virus (HIV), highlights the importance of influenza vaccination in these people. Therefore, the current study aimed to investigate the antibody responses to influenza vaccine in this group. Two hundred subjects were recruited, during autumn 2010 and 2011, to receive, trivalent inactivated influenza vaccine consisting of A (H1N1), A (H3N2), and B strains. Hemagglutination inhibition assay was used to measure the antibody titer against all strains of the vaccine prior and one month post vaccination. Seroconversion rate for A (H1N1), A (H3N2), and B were found to be 58.5%, 67% and 64.5%, respectively. No correlation was found between antibody titer and demographics factors such as age and gender; however, we found a significant correlation between antibody titer and CD4 cell count. Checking the local and systemic reactions after vaccination, the pain on the injection site and myalgia were the most common local and systemic reactions with 20% and 6.5%, respectively. As vaccination with influenza mount considerable antibody responses in HIV-infected patients, annul influenza vaccination seems to be rational in order to prevent or reduce the severe clinical complications induced by influenza virus.

Acta Medica Iranica, 2013; 51(3): 148-152.

Key words: Adverse events; Antibody response; HIV; Influenza; Vaccination

Introduction

Influenza, an acute respiratory disease, is caused by influenza viruses and often characterized with general symptoms such as fever, muscular pain, cough ~~(1)~~ and pneumonia, which is considered as an important clinical complication (1). Patients with immunodeficiency such as HIV are considered to be at the higher risk of serious influenza-associated complications (2-5). Although HIV does not directly influence the humeral immune system, the impairment of B cell function has been reported in these patients (6). In this regard, the slow response of B cells to influenza vaccine has been noticed in HIV-infected patients who have a low CD4 cell count and high viral load. Interestingly, this slow response has been shown to be reinforced by annual influenza vaccination (7).

There are several studies looking at the immunogenicity of influenza vaccines. For example, in the study carried out by Nelson *et al*., the seroconversion rate after influenza vaccination was shown to be lower in HIV-infected patients (52-89%) compared to non-HIV infected patients (94-100%) (8). In another study performed on HIV-infected children, the rate of seroconversion against H1N1 and B were shown to be 70.8% whereas this rate was 54.1% for H3N2 (9).

Additionally, the rate of seroconversion after influenza vaccination has been reported to be around 60-70% in HIV-infected patients (8-10). Regardless of valuable data obtained in the context of the immunogenicity of influenza vaccine in HIV-infected patients, yet there is no data available in Iranian patients who were infected with HIV. Therefore, this study aimed to investigate the antibody responses as well as vaccine safety in these patients vaccinated with

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influenza.

Patients and Methods

The current study is a clinical trial (before-after study) that was performed at the Counseling Center for Behavioral Diseases of Imam Khomeini Hospital in Tehran during autumn 2010 and 2011. Two-hundred HIV-infected patients were recruited into this study which was approved by the local research ethics committee of the Tehran University of Medical Sciences. A written informed consent was obtained from all patients prior to enrollment and all enrolled patients, who met the inclusion criteria, were subjected to influenza vaccination. The inclusion criteria were age between 18 and 60 years, no sensitivity to influenza vaccine, egg and its derivatives, no clinical sign of acute disease at the time of study, no clinically confirmed influenza infection, no sign of pregnancy, no chronic treatment with immunosuppressive and systemic steroid medications for at least 4 weeks before the study, and the lack of co-infection with tuberculosis, autoimmune disorders and cancer. Additionally, those who had received any vaccination during one month before the study were excluded. Prior to enrollment, demographic and clinical data were collected from all patients.

A trivalent inactivated vaccine (Lyon company, France) containing a mixture of 15 μg of A/California/7/2009 (H1N1), A/Perth/16/2009 (H3N2), and B/Brisbane/60/2008 was used and a volume of 0.5 ml injected into the deltoid muscle of subjects. To assess the antibody responses sera were separated from 5 ml of fresh whole bloods taken from patients and stored at -20 ^{o}C until use. Moreover, the result of CD4 cell count of these patients was obtained from their medical files over three months prior and post vaccination. All patients were monitored over the following week to check if there were any local and systemic reactions. Except for the pain on the injection site, itching, muscular pain, bruising, and fatigue all other reactions were subjected to the direct clinical examination. A month later, patients were all advised to return to the clinic for the measurement of influenza antibody titer. Hemagglutination inhibition (HI) assay was used to measure the antibody titer against all strains of the vaccine. HI antibody titers of ≥1:40, if baseline titers were <1:10 or a ≥4 fold increase in those with baselines titers ≥1:10 were considered as seroconversion. In addition, HI antibody titers ≥1:40 were defined as protective titer. In this regard, the seroconversion and the seroprotection of 40% and 70%, respectively, have been shown to be an indicative of the vaccine's immunogenicity in population (11).

Statistical analysis

Statistical analysis was performed by SPSS (version 18). The quantitative data are reported by mean and standard deviation. Furthermore, Student's t test and Chi-square were used as appropriate to determine the relationship between response to the vaccine and the independent variables. *P*-values of ≤0.05 were considered significant.

Results

The antibody responses to the influenza vaccine were tested in two hundred HIV-infected patients to investigate the seroconversion rate of H1N1, B, H3N2, and protective H1 titer. The demographical and the clinical data of all patients are shown in table 1. The baseline and antibody responses to the vaccine in HIV-infected are shown in table 2. Analyzing the data obtained from seroconversion rate and protective HI titer, no correlation was found between the antibody responses, and the age, gender, smoking, alcohol drinking, illicit drug use, anti retroviral therapy (ART), previous influenza vaccination, and HBV or HCV co-infections.

Table 1. Demographic data and clinical characteristics in HIV- infected patients receiving trivalent inactivated Influenza vaccine.

Characteristic	HIV-infected patients (n=200)
Median age (standard deviation)	35/57 (7/9)
Male/Female ratio	2/38:1
History of smoking	116 (58%)
History of addiction illicit drug	88 (44%)
History of alcohol addiction	44 (22%)
Injecting drug use	75 (37/5%)
Hetrosexual transmission	80 (40%)
Hetro/homosexual transmission/Injecting drug use	34 (17%)
Blood transfusion/blood Products	4 (2%)
History of tattoo	4 (2%)
No identified Risk	3 (1/5%)
Hepatitis B co-infection	18 (9%)
Hepatitis C co-infection	86 (43%)
Median CD4 (Pre-vaccination)	282/43
Median CD4 (Post-vaccination)	276/44
Anti retroviral therapy	175 (72/5%)
Median month anti retroviral therapy before study	17.7

Table 2. Baseline and antibody responses against trivalent inactivated Influenza vaccine in HIV-infected patients (n=200).

Viral Strains	Protective HI titer and Seroconversion rate		Antibody responses; N (%)
A(H/N1)	Protective (≥1:40) HI titer	Pre-vaccination	136 (%68)
		Post-vaccination	184 (%92)
	Seroconversion rate (≥4-fold HI titer rise)		117 (%58/5)
B	Protective (≥1:40) HI titer	Pre-vaccination	136 (%68)
		Post-vaccination	184 (%92)
	Seroconversion rate (≥4-fold HI titer rise)		129 (%64/5)
A(H3N2)	Protective (≥1:40) HI titer	Pre- vaccination	149 (%74/5)
		Post-vaccination	189 (%94/5)
	Seroconversion rate (≥4-fold HI titer rise)		134 (%67)

Table 3. Frequency of adverse events in HIV-infected patients (n=200) who received influenza vaccine.

Characteristics	N (%)
Pain	40 (20%)
Itching	10 (5%)
Redness	5 (2/5%)
Swelling	1 (0/5%)
Myalgia	13 (6/5%)
Headache	6 (3%)
Bruising	4 (2%)
Arthralgia	2 (1%)

Comparing the CD4 cell count obtained pre and post vaccination, no significant difference observed (P=0.062). However, a significant association was found between CD4 cell count and antibody responses specific to H1N1 (P=0.017), B (P=0.03), and H3N2 (P=0.028). Considering the reactions observed upon vaccination, 58.5% (117/200) of patients did not show any reaction to the vaccine. As indicated in table 3, pain and myalgia were the most common adverse events observed in these patients.

Discussion

In order to prevent serious influenza-associated complications, HIV-infected patients are recommended to be annually vaccinated against influenza (12). In the current study, we aimed to investigate the antibody responses to influenza vaccine in a subset of Iranian patients who were HIV infected. We also aimed to check if there is any correlation between the antibody responses of influenza vaccine and the demographical or the clinical factors in this group of patients. In order to minimize the potential confounders, we excluded patients who either suffered from co-infections such as tuberculosis or received any vaccine one month prior enrollment into the study.

Consistent with the previously published (13), no correlation was found between the antibody responses to influenza vaccine and demographic data such as age and gender. In addition, we observed no correlation between HBV and HCV co-infections and seroconversion rate.

However, a significant correlation was found between the antibody responses and the CD4 cell count. Our data was consistent with the previously published data (7,14). The association between the antibody responses to the influenza vaccine and HIV viral load has also been reported by Evison *et al.* (15). In terms of seroconversion rate, we could not found a significant difference between those patients who received ART and naïve HIV-infected patients. This result was contrary to the findings by Madhi *et al.* in which a higher seroconversion rate has been observed in the group who had received ART (16). Short term treatment with ART might be a possible reason behind this controversy.

Further to check the protective H1 titers in these patients, we found a higher titers in response to trivalent influenza vaccine (92% for H1N1 and B; 94.5% for H3N2) compared to the study carried out by Vigano *et al.* where the protective HI titers for H1N1, B, and H3N2 were shown to be 79.2%, 75%, and 79.2%, respectively (9). It is worth to note that in the mentioned study, they have also obtained lower protective titers before vaccination. The highest seroconversion rate was also achieved for H3N2, indicative of high incidence of H3N2 influenza in our society during last year. Differences in the immunogenicity of vaccine strains might be one of the reasons behind this elevated H3N2 seroconversion.

In our setting the vaccine had no clear effect on CD4 cell count which was consistent with the previously published data (16-18). Moreover, similar to the previously published data by other groups (19,20), the most common local and systemic reactions recorded

after vaccination was pain on the injection site and myalgia at the frequency of 20% and 6.5%, respectively.

All together, the influenza vaccination of HIV-infected patients was found to be a safe procedure resulting from sufficient level of antibody responses and trivial local or systemic reactions. However, further investigation needs to be performed to evaluate the efficacy of influenza vaccine in HIV-infected patients and vaccine immunogenicity in the context of co-infection such as tuberculosis.

Acknowledgments

The authors would like to thank Dr. Gholam Reza Javid for his helpful comments.

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