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Safety and immunogenicity of an inactivated whole-virion chromatographic vaccine with aluminum against influenza A (H1N1) pdm09: A randomized, blinded, dose-dependent placebo-controlled clinical study

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Abstract

1. Background

The pandemic influenza A/H1N1 pdm09 emerged in 2009 and led to high demand for influenza vaccines, highlighting the limited vaccine manufacturing capacity world-wide. To meet the needs of Kazakhstan for an effective vaccine against pandemic influenza, the Research Institute for Biological Safety Problems developed an inactivated whole-virion chromatographic vaccine with aluminum (trade name Refluvac). This paper presents the results of a clinical Phase I single-use study of the vaccine in healthy volunteers aged 18-60 years.

2. Materials and methods

The study was conducted at the clinical facilities of the Research Institute of Influenza (Russian Federation). Number of volunteers enrolled in the study - 54 people, including those who receive three doses (3.75, 7.5 or 15.0 mcg of hemagglutinin [HA]) of the vaccine - 36 people (to 12 people in each dose) and a placebo - 18 people. Antibody response (seroconversion and seroprotection rates, geometric mean titer [GMT], seroconversion factors) was determined using the hemagglutination inhibition (HAI) assay. Cellular immune response was assayed using the index of stimulation of peripheral blood mononuclear cells (PBMCs) and the production of cytokines by antigen supernatant-stimulated cells. Reactogenicity and safety were assessed by monitoring adverse reactions (local and systemic reactions), physical examinations, monitoring of vital symptoms and laboratory tests (general and biochemical blood tests, Ig E, urinalysis). The study was conducted in accordance with protocol VRK-I-00-01/2010 approved by the Federal Service on Surveillance in Healthcare and Social Development of the Ministry of Health and Social Development of the Russian Federation.

3. Results

Volunteers vaccinated with the vaccine at a dose of 3.75 mcg HA adverse events related to vaccination were not observed. Volunteers vaccinated with the vaccine at a dose of 7.5 mcg HA did not have any systemic reactions related to the vaccination. Weak local reactions, presenting as pain and discomfort at the injection site, were observed in 3 of the 12 (25%) volunteers vaccinated at a dose of 7.5 mcg HA; these reactions were not accompanied by the development of hyperemia or infiltrates, were transient (lasted no more than 2 days), and disappeared without medication. Among the volunteers vaccinated with the vaccine at a dose of 15.0 mcg HA, one medium systemic reaction was observed as an increase in temperature up to 37.8°C after 6 hours post vaccination (PV). Weak local reactions, presenting as pain and discomfort at the injection site were not observed in volunteers vaccinated at a dose of 15.0 mcg HA. Clinical and laboratory examinations of the volunteers on days 7 and 21 PV revealed that the morphological and biochemical parameters of peripheral blood, including the total level of IgE, did not significantly alter from normal physiological values (all $p>0.05$). Vaccination had no adverse effect on electrocardiogram (ECG) data PV, as the ECG data for all volunteers remained similar to the baseline values. In terms of rating the immunogenic activity of the vaccine, 83.3% of the volunteers vaccinated at a dose of 3.75 mcg HA had a 4-fold seroconversion rate; the seroprotection rate was 75%, the multiplicity of growth of the antibody titer was 10.7 and the GMT was 53.4. In the group vaccinated at a dose of 7.5 mcg HA, 100% of the volunteers had a 4-fold seroconversion rate; the seroprotection rate was 75%, the multiplicity of growth of the antibody titer reached 32.0, and the GMT was 160.0. Using a high dose of the vaccine (15.0 mcg HA), an increase in the proportion of people (from 75% to 83%) with protective antibody titers, but increase the GMT and the multiplicity of growth of the antibody titer in this group compared to group, which vaccinated at a dose of 7.5 mcg HA was not observed ($p>0.05$).

Vaccination led to the formation of a cellular immune response, which was polarized towards Th-1 production.

4. Conclusions

This Phase I clinical study of the Refluvac vaccine at doses of 3.75, 7.5 or 15.0 mcg HA in healthy volunteers aged 18-60 years-old indicates the antibody can induce pronounced immunogenicity, is well tolerated, has a low reactogenicity, is safe, and leads to the formation of a cellular immune response.