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ИЗУЧЕНИЕ ОСНОВНЫХ ПАРАМЕТРОВ ИММУНОГЕННОСТИ ВАКЦИНЫ «УЛЬТРИКС»

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Цель. Клиническое исследование вакцин «Ультрикс» производства ООО «ФОРТ» с содержанием разных серотипов вирусов гриппа: штаммов H1N1 A/California/7/2009 (H1N1) pdm 09, H3N2 A/HongKong/4801/2014, NYMCX-263B(15/184) и B/Brisbane/60/2008 NYMCBX-35 (15/300) Victorialineage (эпидемиологический сезон 2016 г.) и штаммов H1N1 A/Michigan/45/2015 NYMCX-275 (16/248), H3N2 A/HongKong/4801/2014, NYMCX-263B(15/184) и B/Brisbane/60/2008 NYMCBX-35 (15/300) Victorialineage (эпидемиологический сезон 2017 г.).

Материалы и методы. Изучение основных параметров иммуногенности включало определение уровня среднегеометрического титра антител, серопротекции и сероконверсии и относительное количество лиц с 4-кратным увеличением титра антител после вакцинации. Иммуногенность определяли микрометодом в реакции торможения гемагглютинации. Сыворотки тестировали с диагностикумами из серотипов вируса гриппа идентичных вакцинным штаммам.

Результаты. Уровень серопротекции «Ультрикс» составил 91,7-95,8% (2016) и 93,8-97,9% (2017). Максимальный уровень серопротекции достигнут через 6 месяцев при вакцинации «Ультрикс», содержащей серотип H1N1A/California. Выявлено повышение среднегеометрического уровня анти-НА в 2,55-4,36 раза ко всем вакцинным штаммам при вакцинации в 2016 и 2017 гг., 4х-кратное увеличение титров антител у более 70% добровольцев через 21 день после первой иммунизации в 2016 г.

Заключение. Полученные результаты клинических исследований вакцины «Ультрикс» с разным антигенным составом подтверждают соответствие параметров иммуногенности препарата требованиям Комитета патентованных медицинских продуктов (CPMPEMEA, CPMP/EWP/1045/01) и Государственной фармакопеи РФ XIII издания (ГФ РФ XIII).

Ключевые слова: *вакцина «Ультрикс»; серопротекция; сероконверсия; иммуногенность; антигенный импринтинг.*

A STUDY OF THE MAIN PARAMETERS OF IMMUNOGENICITY OF ULTRIX VACCINE

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Aim. Clinical trial of Ultrix vaccine of OOO FORT manufacture containing different serotypes of influenza virus: H1N1 A/California/7/2009 (H1N1) pdm 09, H3N2 A/HongKong/4801/2014, NYMCX-263B(15/184) and B/Brisbane/60/2008 NYMCBX-35 (15/300) Victorialineage strains (epidemiological season of 2016) and H1N1 A/Michigan/45/2015 NYMCX-275 (16/248), H3N2 A/HongKong/4801/2014, NYMCX-263B(15/184) иB/Brisbane/60/2008 NYMCBX-35 (15/300) Victorialineage strains (epidemiological season of 2017).

Materials and Methods. A study of the basic parameters of immunogenicity included determination of the geometric mean value of the antibody titer, of seroprotection and seroconversion and of relative number of individuals with 4-fold increase in the antibody titer after vaccination. Immunogenicity was determined by a micromethod in hemagglutination inhibition reaction. Sera were tested with diagnosticums obtained from serotypes of influenza virus identical to vaccinal strains.

Results. The level of seroprotection with Ultrix made 91.7-95.8% (2016) and 93.8-97.9% (2017). The maximal level of seroprotection was achieved in 6 months after vaccination with Ultrix containing H1N1A/California serotype. 2.55-4.36-Fold increase in the geometric mean value of anti-HA to all vaccinal strains was found in vaccination in 2016 and 2017, and 4-fold increase in antibody titer in more than 70% of volunteers on the 21st day after the first immunization in 2016.

Conclusion. The obtained results of clinical trials of Ultrix vaccine with different antigenic composition confirms the correspondence of the immunogenicity parameters of the drug to the requirements of the Committee for Proprietary Medical Products (CPMPEMEA, CPMP/EWP/1045/01) and of State Pharmacopoeia of RF of XIII edition (SP SP XIII).

Keywords: *Ultrix vaccine; seroprotection; seroconversion; immunogenicity; antigenic imprinting.*

Influenza remains one of the most common infectious diseases with a high risk of development of threatening complications [1-3]. Appearance of new serological variants of the influenza virus, for example, of A/H1N1/A/California/7/2009 strain in 2009, led to development of moderate and severe forms of influenza [1,4] with the underlying evident immune suppression followed by development of multiorgan failure [5] associated with high lethality [4]. At present the most effective and available instrument for reduction of the risk of infections and of related complications is use of influenza vaccines [6-8]. As a rule, control of influenza morbidity with immunobiological drugs has several aspects. On the one hand, the immune system of a particular individual differently responds to circulating strains of virus and to the strains encountered by it for the first time, if they have antigenic similarity [7,9, 10]. On the other hand, formation of postvaccinal immunity, persistence of antibodies to viral H- and N-glycoproteins depends on such parameters as immunogenicity of influenza vaccine [4,11,12]. Immunogenicity of influenza vaccines and dynamics of reduction of anti-influenza antibody titers remains a subject of numerous research works in view of variety of influenza vaccines in the pharmaceutical market.

Aim – to evaluate immunogenicity of inactivated split influenza Ultrix vaccine (ЛСР-001419/08) with different antigenic composition of vaccinal strains in 21 days, 6 months, 10 months, and to determine the period of persistence of antihemagglutinating antibodies (anti-HA) after vaccination.

Materials and Methods

In the clinical trial 48 volunteers participated (signed informed consent in accordance with the normative documents)

at the age from 18 to 60 years (n=48) (mean age – 35±8.2 years), who were vaccinated in September 2016 and in May 2017 with Ultrix preparation produced by OOO FORT. The vaccine was prepared with H1N1 A/California/7/2009 (H1N1) pdm 09, H3N2 A/HongKong/4801/2014, NYMCX-263B (15/184), B/Brisbane/60/2008 NYMCBX-35 (15/300) Victorialineage strains recommended by WHO for epidemiological season of 2016, and H1N1 A/Michigan/45/2015 NYMCX-275 (16/248), H3N2 A/HongKong/4801/2014, NYMCX-263B (15/184), B/Brisbane/60/2008NYMCBX-35 (15/300) Victoria-lineage strains recommended for epidemiological season of 2017, and contained 15 μg hemagglutinin of each strain. The level of antibodies in blood sera was determined by a mictomethod in hemagglutination inhibition reaction (HIR) in accordance with State Pharmacopoeia of RF of XIII edition (SP SPXIII) [13]. The reaction was conducted with influenza diagnosticums obtained from influenza virus strains used for production of vaccine for the respective epidemiological season. Non-specific hemagglutination inhibitors were removed from the immune sera using RDE-reagent (Deben Diagnostics Ltd., United Kingdom). The study was conducted with use of microplates (96-well V-shaped plates) by method of paired sera on the 21st day, then in 6 and 10 months after vaccination of volunteers. Hemagglutinin titer less than 1:10 was evaluated as 1:5. Effectiveness of Untrix vaccines was evaluated by immunogenicity criteria (Table 1).

Statistical processing of the data was conducted using Statistica 6.0 program package.

Table 1

Criteria of Immunogenicity of Influenza Vaccines*

Criteria of Immunogenicity	Value
Seroconversion factor (increase in the geometric mean of antibody titers on the 21th day as compared to the initial level), expressed in multiplicity of increase	>2.5
Seroconversion level (percentage of volunteers with more than 4-fold increase in the antibody titer compared to the initial level)	>40%
Seroconversion level (percentage of individuals with antibody titer 1:40 on the 21st day after vaccination)	>70%

Note: *According to the data of Committee for Proprietary Medical Products (CPMPEMEA, CPMP/EWP/1045/01) and SP SP XIII

Results and Discussion

Before vaccination in 2016 the number of seronegative sera tested with H1N1 A/California/7/2009 (H1N1)pdm09 diagnosticum was 12 (25,0%); with H3N2 A/HongKong/4801/2014 (H3N2) – 14 (29.2%); with B/Brisbane/60/2008 – 11 (22.9%). Absence of antibodies to three vaccinal strains of Ultrix was found in 2 volunteers (4.2%). A high percentage of seropositive sera, with the absence of the data about preceding vaccination, as a rule, confirms the fact of active influence of the virus on the immune system of an individual in the period of its circulation, and indicates correspondence of the antigenic composition of vaccines to the structure of the subtype of the influenza virus spread in the period of vaccination [7]. A relative amount of volunteers with seroconversion among seronegative (antibody titer 1:20 and less) and seropositive (antibody titer 1:40 and more) individuals in 21 and 180 days after vaccination with Ultrix are given in Table 2.

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Table 2

Range of Antibody Titers, Amount of Volunteers with Seroconversion among Seronegative and Seropositive Individuals

Number of Volunteers before Vaccination (%) (range of antibody titers)	**Antigenic Variant of Strains**					
	H1N1A/California		**H3N2A/HongKong**		**B/Brisbane**	
	А	Б	А	Б	А	Б
	12 (25%)	36 (75%)	14 (29.25%)	33 (68.75%)	11 (22.9%)	37 (77.1%)
in 21 day after vaccination						
Amount of volunteers with seroconversion (%) (range of antibody titers)	10 (83.3%) (1:40-1:320)	25 (69.4%) (1:40-1:1280)	12 (85.7%) (1:80-1:640)	25 (75.75%) (1:40-1:640)	8 (72.3%) (1:20-1:320)	27 (72.97%) (1:40-1:640)
Pf	> 0.05		> 0.05		> 0.05	
in 180 days after vaccination						
Amount of volunteers with seroconversion (%) (range of antibody titers)	10 (83.3%) (1:40-1:320)	16 (44.4%) (1:160-1:640)	6 (42.9%) (1:20-1:640)	11 (33.3%) (1:160-1:320)	5 (45.5%) (1:80-1:160)	7 (18.9%) (1:160-1:6400)
Pf	< 0.05		> 0.05		< 0.05	

Note: А – seronegative; В – seropositive; Pf – Fisher angular transformation

In general, in the majority of volunteers vaccinated in 2016, evident activation of the immune system was noted with formation of strong and comparable in duration immunity to all strains of Ultrix vaccine. After 21 days, in 35 (72.9%) of the vaccinated individuals, seroconversion to H1N1A/California and B/Brisbane strains was found, in 37 (77.1%) – to H3N2A/HongKong strain. Comparative analysis of the relative amount of sera with seroconversion among seronegative and seropositive volunteers in 21 days did not reveal any connection between the appearance of influenza antibodies in 1:40 and higher titers and the initial level of antibodies before vaccination. Despite a higher amount of individuals with seroconversion among seropositive volunteers – 25 and 27 individuals to A(H1N1), A(H3N2) and B strains, respectively, this difference appeared to be statistically unreliable (Pf >0.05). An exception was immune response to antigenic variants of A(H1N1) and B strains in seronegative and seropositive volunteers in 6 months. Irrespective of the initial level of antibodies, the number of volunteers with seroconversion (83.3 and 45.5%) was statistically reliably higher in the group of volunteers with antibody titer before vaccination 1:20 and less than in the group of seropositive volunteers (Pf < 0.05).

Geometric means of anti-HA titers ($geom_m$) on the 21st day after a single immunization, were 173.5; 135.7 and 88.5, forming seroprotection to A(H1N1), A(H3N2) and B strains of virus in 95.8, 91.7 and 93.7% of the volunteers, respectively.

A higher antigenicity was found in H1N1A/California strain, which was confirmed by activation of the immune system within 6 months after a single immunization, and by increase in the level of seroprotection to 100%. In the same period, the amount of seropositive sera to H3N2A/HongKong and B/Brisbane gradually reduced to 85.4 and 91.7%, respectively, with preservation of a high level of protection in accordance with the requirements of CPMPEMEA and CPMP/EWP/1045/01 (Table 1).

Volunteers vaccinated in 2017 and repeatedly vaccinated in 10 months with Ultrix vaccine in which H1N1A/California strain was replaced with H1N1A/Michigan strain,

responded to H3N2A/HongKong and B/Brisbane strains by less intense increase in the antibody titer than on the first contact with antigens of vaccinal strains. The amount of seropositive sera with H3N2A/HongKong and B/Brisbane antibodies increased after the first antigenic stimulation 3.1 and 4.1-fold and in repeated stimulation only 2.4 and 2.5-fold, respectively (Pf<0.001 and Pf<0.05). Vaccination with H1N1A/Michigan strain in 2017 evoked production of antibodies in 1:40 titer in a higher amount of volunteers (97.9%). With this, a higher percentage of individuals with seropositive sera does not characterize H1N1A/ California strain as immunogenic, since the amount of seronegative sera to H1N1A/ Michigan strain before vaccination was 1.4 times less than to H1N1A/California strain.

Repeated vaccination with Ultrix in 10 months (2017) stimulated production of antibodies to the antigens of the virus identical to those in vaccines of 2016 and 2017, in lower titers than to H1N1A/Michigan strain. Maximal titers 1:640 to H3N2A/HongKong strain after the first vaccination were determined in 4 volunteers (4.2%), 4-8-fold increase in antibody titers was noticed in 62.5% of volunteers. Repeated vaccination with the same strain stimulated production of antibodies in titers not exceeding 1:320 in 5 (10.4%) individuals, absence of seroconversion characterrizing low activity of the immune system was found in 29 (60.4%) volunteers, and 4-8-fold increase in antibody titers was found in a considerably smaller amount of volunteers (35.4%). 4-8-Fold increase in anti- HA titers to B/Brisbane strain in repeated immunization was identified in 12 sera which is 2.7 times less than after the first immunization (25% in 2017 and 66.7% in 2016).

Maximal increase in antibody titers to 1:1280 to H1N1A/California was determined in one serum (2.1%). In more than 50% of sera the titers increased 4-8-fold which made 39.6-18.7%. Antibodies to H1N1A/ Michigan in the maximal titer 1:320 were also found in one serum (2.1%), seroconversion was noted in 41.7% of volunteers. The analysis of the relative amount of sera with multiple increase in anti-HA titers to H1N1A/ California and H1N1A/Michigan did not reveal any statistically significant differences in the level of seroconversion (Pf>0.05) despite the differences in the level of seroprotection (70.8% and 41.7%, respectively) which confirms similar antigenic composition of A/H1N1 vaccinal strains of different origin. Comparative data for the quantity of seronegative sera and sera with seroconversion are given in Table 3.

Table 3

Structure of Seronegative and Seropositive Sera in 2016 (in 21 and 180 days) and in 2017 (in 21 days after vaccination)

Time after Vaccination/Antigenic Variant of Strains	Multiplicity Factor for Increase in Antibody Titers abs/%					
	0	2	4	8	16	32
(21 days) /H1N1A/California*	7/14.6	7/14.6	19/39.6	9/18.8	4/8.3	2/4.2
/H3N2A/HongKong*	9/18.8	4/8.3	23/47.9	7/14.6	4/8.3	1/2.1
/B/Brisbane*	5/10.4	8/16.7	22/45.8	10/20.8	3/6.3	–
(6 months) /H1N1A/California*	10/20.8	13/27.1	13/27.1	8/16.7	3/6.3	1/2.1
H3N2A/HongKong*	15/31.3	15/31.3	13/27.1	2/4.2	2/4.2	1/2.0
B/Brisbane*	20/41.7	17/35.4	7/14.6	1/2.1	2/4.2	1/2.1
(21 days) /H1N1A/Michigan**	12/25.0	16/33.3	18/37.5	1/2.1	–	1/2.1
/H3N2A/HongKong**	14/29.2	15/31.3	13/27.1	4/8.3	16/4.2	–
/B/Brisbane**	17/35.4	16/33.3	8/16.7	4/8.3	3/6.3	–

Примечание: * – 2016 season, ** – 2017

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A small amount of volunteers (from 5 to 9) were identified with immunological tolerance to B/Brisbane and H3N2A/Hong Kong strains, respectively. In more than 50% of vaccinated individuals 4-8-fold increase in antibody titers was found (58.4% of individuals with H1N1A/California antibodies; 62.5% with H3N2A/HongKong antibodies and 66.6% – with B/Brisbane–antibodies), which is significant for formation of individual and collective immunity to influenza virus. Repeated testing of sera in 6 months showed increase in the amount of volunteers with the absence of antibody titer, and reduction in the quantity of sera with preserved 4-8-fold increase in the antibody titer. For example, the amount of vaccinated individuals with the absence of antibodies to B/Brisbane strain in 6 months increased 4-fold, and the amount of the volunteers with 4-8-fold increase in the antibodies to this strain decreased from 66.6% to 16.7%. A non-uniform reaction of the immune system to the heterogenetic and new antigens in different vaccines is associated with the immune phenomenon of the antigenic imprinting which consists in construction of a stronger immune response on repeated contact with the antigen that was first memorized by the immune system [9,10]. In the given clinical trial it was rather difficult to identify the strain that caused antigenic imprinting not only because of a wide circulation of certain serotypes of influenza virus in nature [3] within decades, but also because of use of different strains of H1N1 serotype of influenza A virus in the vaccine that have been recently used for seasonal vaccination [11,12].

In comparison of geometrical means of multiplicity factor of increase in the antibody titers, no statistically significant differences in the antigenicity of vaccinal strains were found. However, a statistically significant 2.55- and 4.36-fold increase in $geom_m$ of anti- HA was found ($Pf<0.05$) as compared to the initial antibody titer before vaccination (Table 4).

Table 4

$Geom_m$ Values of Multiplicity Factor of Increase in Anti-HA in 21 Days after Vaccination in Different Years

Immunogenicity Criterion	2016			2017		
	H1N1A/California	H3N2A/HongKong	B/Brisbane	H1N1A/Michigan	H3N2A/HongKong	B/Brisbane
$Geom_m$ of multiplicity factor of increase in anti-HA* titers	4.36	3.89	3.89	2.63	2.51	2.55
Friedman test	<0.01	<0.01	<0.01	<0.05	<0.05	<0.05

Note: * – Multiplicity of increase in geometric means of antibody titers to different antigenic variants of influenza virus in sera of volunteers after immunization with Ultrix vaccine

The level of differences between anti-HA titers in different periods after vaccination was determined by Friedman test that was used for comparison of four measurement conditions (antibody titer before vaccination, in 21, 180 days and 10 months) for 48 (n) examined sera. The empiric value $X_r^2=70.05938$ reflects considerable discrepancy of rank sums. At the significance level $x^2 0.05$ and $x^2 0.01$ equaling 7.81 and 11.34, respectively, nonrandom differences between antibody titers were confirmed that were pro-

duced in different periods of time after vaccination that reach maximum in 6 months.

Conclusion

Thus, clinical study of Ultrix influenza vaccine with evaluation of construction of immune response showed conformity of the immunobiological preparation with the main criteria of immunogenicity. Ultrix vaccine provides seroprotection level in more than 90% of vaccinated individuals in 21 days and more than 2.5-fold increase in the geometrical mean of the influenza antibody titer in comparison with the initial level.

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