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A Clinical Study of the Safety and Tolerability of Live Nasal Vaccines for the Prevention of Pertussis

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Abstract

Introduction. Due to the growth of laboratory-confirmed cases of pertussis among adolescents and adults, the spread of latent form of disease and the identification of asymptomatic carriage of the pathogen, the need arose to create a new vaccine against *B. pertussis*. On the basis of N. F. Gamaleya Federal Research Center for Epidemiology & Microbiology, a pertussis vaccine, containing attenuated *B. pertussus* bacteria, was developed. The article presents data on a clinical trial of the first phase of the pertussis vaccine "GumGVK, live intranasal vaccine for the prevention of pertussis" in healthy volunteers. Based on the results of the study, data shows the safety and tolerability of the first intranasal vaccine using on humans.

Aim. To Study the safety and tolerability of the vaccine "GamGVK, live vaccine for intranasal use for the prevention of whooping cough»

Materials and methods. Volunteers who expressed a desire to participate in the study were informed about its goals and objectives, conditions and requirements for participants, including the criteria for their inclusion/exclusion from the study. After signing the informed consent, the volunteers were screened for their compliance with the inclusion criteria. Screening studies and safety assessment of the drug were performed on the basis of anamnesis, subjective complaints, assessment of vital signs, ECG, peak flowmetry, results of laboratory tests of urine and blood, enzyme immunoassay of blood serum, analysis of nasopharyngeal aspirates for the presence of pertussis pathogen DNA, results of physical examination.

Results and discussion. The study involved 36 "healthy" volunteers aged 18–40 years. The average age of the volunteers was 26.2 ± 5.5 years. Not reliably identified AES associated with the use of GumGVK. None of the used doses of the drug led to the formation of local and General allergic reactions to intranasal administration of GumGVK.

Conclusions. The drug GumGVK is safe for nasal use, has good tolerance.

Keywords: pertussis, live vaccine, anti-pertussis vaccine.

Conflict of interest: no conflict of interest.

Contribution of the authors. Gennadij I. Karataev, Alisa Yu. Medkova, Lyudmila N. Sinyashina developed the design of the clinical trial Protocol. Alevtina A. Lidzhieva, Ludmila V. Kolobukhina, Irina S. Kruzhkova, Liliya N. Merkulova, Natalia A. Antipyat, Svetlana V. Smetanina performed the work for a clinical trial. Gennadij I. Karataev, Alisa Yu. Medkova, Evgenij G. Semin, Lyudmila N. Sinyashina, Alevtina A. Lidzhieva, Rezida A. Sioundioukova participated in data interpretation. All authors participated in the discussion of the results and writing the text of the article.

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Клинические исследования безопасности и переносимости живой вакцины интраназального применения для профилактики коклюша

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Резюме

Введение. В связи с ростом лабораторно подтвержденных случаев коклюша среди подростков и взрослых, распространением стертых форм и выявления бессимптомного носительства возбудителя возникла необходимость в создании новой вакцины против *B. pertussis*. На базе ФГБУ «НИЦЭМ им. Н. Ф. Гамалеи» была разработана противококлюшная вакцина, содержащая аттенуированные бактерии *B. pertussus*. В статье представлены данные по клиническому исследованию I фазы противококлюшной вакцины «ГамЖВК, живая вакцина интраназального применения для профилактики коклюша» на здоровых добровольцах. По результатам исследования представлены данные о безопасности и переносимости интраназальной вакцины при первом применении у человека.

Цель. Изучение безопасности и переносимости вакцины «ГамЖВК, живая вакцина интраназального применения для профилактики коклюша».

Материалы и методы. Добровольцы, изъявившие желание участвовать в исследовании, были проинформированы о его целях и задачах, условиях и требованиях к участникам, в том числе о критериях их включения/исключения из исследования. После подписания информированного согласия был проведён скрининг добровольцев на их соответствие критериям включения. Скрининговые исследования и оценку безопасности препарата ГамЖВК проводили на основании анамнеза, субъективных жалоб, оценки жизненно важных показателей, ЭКГ, пикфлоуметрии, результатов лабораторных исследований мочи и крови, иммуноферментного анализа сыворотки крови, анализа назофарингеальных аспиратов на наличие ДНК возбудителя коклюша, результатов физикального осмотра.

Результаты и обсуждение. В исследовании участвовали 36 «здоровых» добровольцев в возрасте 18–40 лет. Не выявлено нежелательных явлений (НЯ) достоверно связанных с применением ГамЖВК. Ни одна из использованных доз препарата не приводила к формированию местных и общих аллергических реакций на интраназальное введение ГамЖВК.

Заключение. Первая фаза слепого, плацебо-контролируемого клинического исследования показала безопасность и хорошую переносимость препарата ГамЖВК при назальном применении на здоровых добровольцах.

Ключевые слова: коклюш, клиническое исследование, противококлюшная живая вакцина, безопасность, переносимость.

Конфликт интересов: конфликта интересов нет.

Вклад авторов. Г. И. Каратаев, А. Ю. Медкова, Л. Н. Синяшина разработали дизайн протокола клинического исследования. А. А. Лиджиева, Л. В. Колобухина, И. С. Кружкова, Л. Н. Меркулова, Н. А. Антипят, С. В. Сметанина выполняли работы по клиническому исследованию. Г. И. Каратаев, А. Ю. Медкова, Г. Е. Семин, Л. Н. Синяшина, А. А. Лиджиева, Р. А. Сюндюкова проводили интерпретацию результатов. Все авторы принимали участие в обсуждении результатов и написании текста статьи.

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INTRODUCTION

During the last decade, the significant growth of laboratory confirmed pertussis cases among adolescents and adults [1–3], distribution of latent forms, asymptomatic *B. pertussis* carriers were found [2, 4, 5]. In the USA where the coverage of children with DTaP vaccination is close to 95 %, since 2000s, the considerable growth of the reported pertussis cases approaching to the pre-vaccination period [6, 7]. The incidence grows in Italy and England [8, 9]. The growth of the reported pertussis cases was observed in Saint Petersburg and Moscow, with the incidence level preserved in Russia [10, 11]. In the current year, 30 % growth of the incidence was found compared to the previous year.

Nowadays, products of DTP vaccine containing the corpuscular pertussis vaccine (CPV) or acellular pertussis vaccine (APV) combined with inactivated diphtheria and tetanus toxins called DTaP are used globally. CPV or APV are sometimes used as mono-vaccines. There are polyvaccines containing hepatitis B antigen, along with DTP. Despite high efficacy of DTP containing CPV, the practice of its use shown adverse effects, APV product containing several purified antigens of the pertussis microbe was offered. It is considered that APV is less toxic, but the direct primate studies have shown that it does not provide antibacterial immunity and protect animals from the experimental pertussis infection [12]. The results of its determination in the comparative test of incidence rates in the vaccinated and unvaccinated populations shows inefficacy of APV revaccination [13, 14].

Another important drawback of the modern pertussis vaccines is the short-term immunity. The ex-

perience of the efficacy studies of anti-pertussis vaccines of various types has shown that the duration of the post-vaccine immunity does not exceed 5–7 years. After the disease, the hyperimmunity is preserved up to 15 years [15].

All modern pertussis vaccines are administered to children above 2–3 months at least 3 times. Thus, the full vaccination cycle is completed not earlier when a child is 6 months of age which maintains a high risk in the first, the most dangerous for the disease, months of his life.

The growth of pertussis incidence, as well, among older children and adult population, has led to the understanding of the revaccination of adolescents and adults. The necessity of mothers' vaccination and formation of "family immunity" is considered [3, 4, 16, 17]. For the purposes, only APV can be nowadays recommended that, as mentioned above, does not provide protection of children and adults from the infection and infection spread, and, consequently, is almost useless for revaccination, the main objective of which is prevent the disease spread in the population.

Therefore it should be stated that, despite the appropriateness of revaccination of adolescents and adults, nowadays, any vaccine for the purposes is absent. CPV is not recommended by the WHO to adults, and modern APV recommended for the purposes is likely to be ineffective. APV has demonstrated its efficacy and safety as CPV alternative for infant vaccination. Such vaccination controls mortality and the disease severity in infants, the age group most vulnerable for pertussis. However, as well as CPV, it requires 3–4-fold vaccination and does not protect children from the re-infection and disease if a vaccination cycle is not completed.

MATERIALS AND METHODS

Study design. A simple blind study was carried out based on of Approval of the Ministry of Health № 895 dated December 28, 2016. The study participants after obtaining the voluntary informed consent were screened for their compliance to the inclusion criteria: men/women aged 18 to 40 years, with verified diagnosis "Healthy", absence of the specific pertussis antibodies (negative ELISA result in accordance with the manufacturer's instruction of the test system for identification of pertussis antibodies) and B. pertussis DNA in nasopharyngeal smears (PCR method), etc.

In the screening period, volunteers were examined in outpatient settings. In accordance with the study design, 36 volunteers selected were divided into three groups of 12 persons. The volunteers from each group took the vaccine in doses: 2.5×10^8 CFU (group 1), 10^9 CFU (group 2) and 4×10^9 CFU (group 3). Each group consisted of 3 volunteers receiving placebo. The volunteers were enrolled to the study with the escalation of the product dose after evaluation of safety parameters and obtaining a favorable decision of the independent monitoring committee on the dose increase. After a single dose, the observation period for the volunteers was 150 days in outpatient settings.

Product GamGVK and its administration. Study product GamGVK – attenuated B. pertussis lyophylisate 4MKS in a vial. Placebo – a sterile lyophilisate stabilizer for further dissolution in 0.9 % sodium chloride for injections. Prior to the use, 0.9 % sodium chloride solution was administered to a vial in the amount of 0.5–8.0 ml depending on the dose.

The volunteers took placebo/the study product in the box inpatient unit of the infectious department. The product was administered nasopharingeally to each nasal passage subsequently, with the breath for better absorption. After the dosing, a volunteer stayed in the inpatient unit for 48-hour observation; for subsequent safety evaluation, the volunteers came to the clinical center for outpatient visits.

Quantification of B. pertussis DNA in the posterior pharyngeal aspirates with the real-time PCR method (PCR-RT). For the molecular-biological test, the DNA isolated from the posterior pharyngeal smears (aspirates) withdrawn at each volunteer's visit was used. The product remnants after centrifugation were treated with guanidine thiocyanate with subsequent DNA sorbtion on the Promega magnetic sorbent (USA) [12, 13]. To quantify B. pertussis DNA genome equivalents in the posterior pharyngeal aspirates, the developed and validated PCR-RT test system was used [13].

Safety and tolerability evaluation. Safety and tolerability were evaluated at each volunteer's visit on the basis of subjective complaints, changes of vital signs, EGC, peak fluometry, results of laboratory urine and blood tests, physical examination results after obtaining the informed consent.

Allergising activity of GamGVK was evaluated with IgE determination using the ELISA method (JSC "Vector-Best", Russia) after a single intranasal vaccination, the analysis of local reactions and a volunteer's health condition performed at each volunteer's visit.

The volunteer's compliance to the inclusion criteria was determined on the basis of collected medical history and laboratory tests.

The absence of the specific pertussis antibodies was determined with ELISA in accordance with the manufacturer's instruction of test systems RIDASCREEN® Bordetella IgG (r-biopharm, Lot: 11037), RIDASCREEN® BordetellaIgM (r-biopharm, Lot: 12426), RIDASCREEN® BordetellaIgA (r-biopharm, Lot: 13316).

The infectious agent in the volunteers' naso-/oropharynx was determined with the developed PCR-RT method from the oropharyngeal swab material.

The presence of HIV and hepatitis B virus antibodies, presence of HBsAg and syphilis causative agent was determined in the clinical laboratory with the certified methods and test systems.

The signs of alcohol or drug abuse were *determined* on the basis of the physical examination and urine screening for amphetamine, marijuana, morphine, cocaine and methamphetamine metabolism products using the set of strips "ImmunoChrom-5-MULTI-Express" ("MED-EXPRESS-DIAGNOSTICS" LLC, Russia).

Pregnancy, lactation (for women) was determined in urine with test strip "FRAUTEST Express" (AXIOM GmbH, Germany).

External respiration function was determined with peak fluometer MicroPeak (Great Britain) on the screening visit and 24 hours after the dosing.

The electrocardiographic test was performed on multi-channel (12 channels), automatic mode, portable electrocardiograph EK12T "Alton-106 C" ("Altomedika" LLC, Russia).

The parameters of laboratory tests of volunteers' blood and urine were determined in the laboratory of the certified method laboratory in accordance with the approved instructions.

The test results were processed with the descriptive statistics and software GraphPad Prism. The normal distribution was assessed with KS-test. Considering that the distribution of values does not correspond to the Poisson distribution at all time point, and the groups consisted of 9 persons, the non-parametric Mann-Whitney test was used for statistical processing and assessment of significance of difference between IgE median values in the groups.

The number and percentage of volunteers with AE. Their relationship with the study product and severity were determined in accordance with CTCAE version 4.03 [18].

RESULTS AND DISCUSSION

Demographic composition of the volunteers

36 "healthy" volunteers aged 18–40 years participated in the study. The average age of the volunteers was 26.2 ± 5.5 years. There were 44 % men, 56 % women. All volunteers are residents of Moscow or the Moscow Region.

Allergenicity evaluation of GamGVK by total IgE level

Total IgE level in blood is a relative value allowing to evaluate allergenicity of the study product. Immunoglobulins of the class play the essential role in initiation of immediate type hypersensitivity reactions. As a value showing the vaccine allergenicity, the several-fold increase of total IgE level in vaccinated patients compared to the values found on day 0 was accepted (prior to the product or placebo administration) (figure 1).

The distribution of IgE values did not correspond to the Poisson distribution at all time points (in accor-dance with the normal KS-test), due to that, the non-parameteric Mann-Whitney criterion was used for statistical processing.

As the data given above showed, IgE differences between placebo group and volunteers receiving the maximal vaccine dose, were insignificant. As well, no significant difference in IgE values in blood of the volunteers was shown after administration of various vaccine doses (results are not provided). The results and the absence of local, and general allergic reactions indicate that product GamGVK does not have allergising properties.

Evaluation of GamGVK safety and tolerability

The analysis of the early post-vaccine period after three does has not shown any local reactions in any volunteer. One adverse event in the maximal dose was

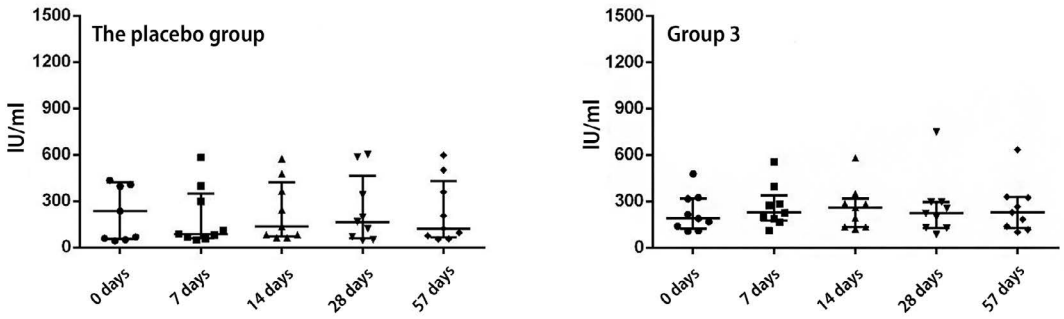

Figure 1. IgE levels in the blood serum of volunteers who received placebo 1A and the maximum dose. Compared with the baseline for the placebo group on the 7th day p = 0.78, on the 14th day 0.78, on the 28th day p = 0.95, on the 57th day p = 0.98; for group 3 p = 0.45, p = 0.65, p = 0.91, p = 0.75 respectively

reported (4×10^9 CFU – group 3) as a short-term increase of body temperature up to 37.1 °C (in point "3 hours" after the dosing), nasal congestion and malaise. The absence of evident clinical signs of ARVI and presence of the temporal relationship with the product allows, by the formal ground, to determine the relationship between the AE and the product as "conditional". However, the absence of local allergic reactions, change of IgE level, as well as, non-compliance of AE picture to clinical signs of the infectious process in pertussis doubts the significance of the AE relationship with the product. Other reported AEs were transient and were related to laboratory abnormalities, did not aggravate in dose escalation and were considered as clinically insignificant per CTCAE classification and not related with the study product. The results of the analysis of AEs and their relationship with the product are summarized in table 1.

Table 1. Total number of volunteers with adverse events vaccinated with different doses of GumGVK and their relationship with the drug.

Parameter	Placebo n = 9		Group 1 2.5×10^8		Group 2 10^9		Group 3 4×10^9	
	n	%	n	%	n	%	n	%
Volunteers with AE	7	77.8	9	100.0	9	100.0	8	88.9
Volunteers with SAE	0	0	0	0	0	0	0	0
Volunteers with AE "defined"	0	0	0	0	0	0	0	0
Volunteers with AE "probable"	0	0	0	0	0	0	0	0
Volunteers with AE "possible"	0	0	0	0	0	0	0	0
Volunteers with AE "questionable"	0	0	0	0	0	0	0	0
Volunteers with AE "conditional"	0	0	0	0	0	0	1	11.1
Volunteers with AE "is not associated"	7	100.0	9	100.0	9	100.0	7	77.8

Table 1 shows that provided such sample size and numerous parameters measured at least one AE mediated by any abnormality of any measured parameter is observed almost in 96 % of the volunteers receiving GamGVK and 78 % receiving placebo. The differences in the number of AEs related to slight abnormalities of laboratory parameters with such sample size (9 in placebo group and 27 in the product group) does not allow to conclude about their significance.

The quantitative analysis of the abnormalities of all measured laboratory parameters in the vaccinated volunteers and in placebo group showed that the absolute values of the abnormalities in most cases did not exceed several percentage from the normal margin, and the percentage of the volunteers with the abnormality among those who received vaccine GamGVK and placebo did not differ for over 0.7–1.5 %. By 14 laboratory parameters, AEs occurred only in the volunteers receiving placebo and were not observed in the subjects who received GamGVK, or found in both groups with similar incidence. The result shows the absence of a significant difference in AEs in the group of vaccinated and placebo subjects and absence of the relationship between AE and the product. The observation over each of the volunteers including the cases of respiratory diseases and one AE conditionally related to cough confirms the conclusion fairness. The described AEs did not have any clinical sequalae and were interpreted as clinically insignificant per CTCAE classification.

CONCLUSION

The first phase of the clinical study aimed to evaluate safety and dose selection of the live intranasal pertussis vaccine for pertussis prevention carried out on 36 healthy volunteers did not show any product-related adverse events. The absence of vaccine reactions (local and general) in 100 % of healthy volunteers suggests good tolerability of GamGVK. In the context of tolerability and safety of "GamGVK, intranasal live vaccine for pertussis prevention", the maximal of the tested product doses can be used on the following stages of the clinical study.

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