Научно-практический журнал
ФАРМАЦИЯ И ФАРМАКОЛОГИЯ

ОРИГИНАЛЬНАЯ СТАТЬЯ

DOI: 10.19163/2307-9266-2023-11-2-137-148

Analysis of cytokine response characteristics and immunopathogenetic effects of double-stranded sodium salt RNA-based drug for postexposure prophylaxis against novel coronavirus infection: double-blind, placebo-controlled trial

O.A. Radaeva[1], L.A. Balykova[1], K.Ya. Zaslavskaya[1], Yu.A. Kostina[1], N.A. Pyataev[1], N.M. Selezneva[1], A.V. Klimova[1], I.Yu. Chegodaeva[1], K.N. Koryanova[2], A.V. Taganov[3], P.A. Bely[4]

[1] National Research Ogarev Mordovia State University,
68, Bolshevistskaya Str., Saransk, Russia, 430005
[2] Pyatigorsk Medical and Pharmaceutical Institute –
branch of Volgograd State Medical University,
11, Kalinin Ave., Pyatigorsk, Russia, 357532
[3] Peoples' Friendship University of Russia,
6, Miklukho-Maklay Str., Moscow, Russia, 117198
[4] Moscow State Medical and Dental University named after A.I. Evdokimov,
Bldg. 1, 20, Delegatskaya Str., Moscow, Russia, 127473

E-mail: radaevamed@mail.ru

Received 02 Feb 2023 | After peer review 14 April 2023 | Accepted 30 April 2023

The aim of the work was to study cytokine response characteristics in the group of persons contacted by a novel coronavirus infection depending on the development of the disease over the next 14 days. Herewith, for the immunocorrection with a preparation based on RNA double-stranded sodium salt (RADAMIN®VIRO) causing a secondary reduction in the risk of COVID-19 in the analyzed group, potential targets had been selected.

Materials and methods. A double-blind, placebo-controlled study of the drug based on RNA double-stranded sodium salt therapeutic effects was conducted in a group of patients who had been in contact with the persons having a confirmed diagnosis of COVID-19. The method of enzyme immunoassay in dynamics was used to determine the content of interferons alpha and beta (IFNα and IFNβ, respectively), interleukin-1β and -10 (IL1β and IL-10, respectively) in the blood serum and saliva in the contact persons, with a retrospective assessment of changes depending on the administration of the drug or placebo, as well as the development of COVID-19.

Results. In the course of the presented study, it was demonstrated that the established content of IFNα (less than 28 pg/ml) and IFNβ (less than 12 pg/ml) in saliva on the 1st–2nd contact days is a predictor of an increased risk of developing COVID-19. Herewith, the increase degree in these immunoregulatory peptides in the interval of 2–3 contact days is important: IFNα and IFNβ allows leveling the negative prognosis in patients by 250% or more. The lowest rates (p <0.001) of INFα on the 1st–2nd contact days, as well as an increase of less than 21% by the 3rd day, were observed in persons with a waist circumference of more than 80/94 cm (women/men). The incidence in this group was higher and amounted to 85% (16 out of 20 people). The predictor role of IL-1β and IL-10 in the blood and saliva in relation to the start of the infectious process was not revealed. The administration of drug based on RNA double-stranded sodium salt to the contact patients made it possible to correct the interferon response in the form of an increase in the content of IFNα and IFNβ, as well as to reduce the incidence in comparison with the placebo group.

Conclusion. Differences in the interferon regulation upon contact with SARS-CoV-2 in the form of lower INF α and β levels, as well as a slightly pronounced growth dynamics in the interval of the first 3 days, influenced the increased risk of developing COVID-19. RADAMIN®VIRO can be recommended as a means of post-exposure prophylaxis of COVID-19 for both medical institutions and for caregivers and / or contacts with COVID-19 patients.

Keywords: coronavirus; COVID-19; RNA double-stranded sodium salt; RADAMIN®VIRO; prevention; interferon inducer

Abbreviations: COVID-19 – an infectious disease caused by the SARS-CoV-2 virus; EAH – essential arterial hypertension; II – interferon inducer; ARI – acute respiratory disease; PCR – polymerase chain reaction; IWRS – Interactive Web Randomization System; eIRC – electronic individual registration card; IFNα – interferon alpha; IFNβ – interferon beta; IL1β – interleukin-1β; IL-10 – interleukin-10; NAAT – nucleic acid amplification test.

For citation: O.A. Radaeva, L.A. Balykova, K.Ya. Zaslavskaya, Yu.A. Kostina, N.A. Pyataev, N.M. Selezneva, A.V. Klimova, I.Yu. Chegodaeva, K.N. Koryanova, A.V. Taganov, P.A. Bely. Analysis of cytokine response characteristics and immunopathogenetic effects of double-stranded sodium salt RNA-based drug for postexposure prophylaxis against novel coronavirus infection: double-blind, placebo-controlled trial. *Pharmacy & Pharmacology.* 2023;11(2):137-148. **DOI:** 10.19163/2307-9266-2023-11-2-137-148

Для цитирования: О.А. Радаева, Л.А. Балыкова, К.Я. Заславская, Ю.А. Костина, Н.А. Пятаев, Н.М. Селезнева, А.В. Климова, И.Ю. Чегодаева, К.Н. Корянова, А.В. Таганов, П.А. Белый. Анализ особенностей цитокинового ответа и иммунопатогенетических эффектов при применении препарата на основе РНК двуспиральной натриевой соли для постконтактной профилактики против новой коронавирусной инфекции: двойное слепое плацебо-контролируемое исследование. Церебропротекторное действие комбинации ситаглиптина с аминогуанидином при нарушениях мозгового кровообращения. *Фармация и фармакология.* 2023;11(2):137-148. **DOI:** 10.19163/2307-9266-2023-11-2-137-148

RESEARCH ARTICLE

ISSN 2307-9266 e-ISSN 2413-2241

Scientific and Practical Journal
PHARMACY & PHARMACOLOGY

Анализ особенностей цитокинового ответа и иммунопатогенетических эффектов при применении препарата на основе РНК двуспиральной натриевой соли для постконтактной профилактики против новой коронавирусной инфекции: двойное слепое плацебо-контролируемое исследование

О.А. Радаева[1], Л.А. Балыкова[1], К.Я. Заславская[1], Ю.А. Костина[1], Н.А. Пятаев[1], Н.М. Селезнева[1], А.В. Климова[1], И.Ю. Чегодаева[1], К.Н. Корянова[2], А.В. Таганов[3], П.А. Белый[4]

[1] Федеральное государственное бюджетное образовательное учреждение высшего образования «Национальный исследовательский Мордовский государственный университет им. Н.П. Огарёва», 430005, Россия, г. Саранск, ул. Большевистская, д. 68

[2] Пятигорский медико-фармацевтический институт – филиал федерального государственного бюджетного образовательного учреждения высшего образования «Волгоградский государственный медицинский университет» Министерства здравоохранения Российской Федерации, 357532, Россия, г. Пятигорск, пр-т Калинина, д. 11

[3] Федеральное государственное автономное образовательное учреждение высшего образования «Российский университет дружбы народов», 117198, Россия, г. Москва, ул. Миклухо-Маклая, д. 6

[4] Федеральное государственное бюджетное образовательное учреждение высшего образования «Московский государственный медико-стоматологический университет им. А.И. Евдокимова» Министерства здравоохранения Российской Федерации, 127473, Россия, г. Москва, ул. Делегатская, д. 20, стр. 1

E-mail: radaevamed@mail.ru

Получена 02.02.2023 После рецензирования 14.04.2023 Принята к печати 30.04.2023

Цель. Изучение особенностей цитокинового ответа в группе лиц контактных по новой коронавирусной инфекции в зависимости от развития заболевания в течение последующих 14 дней с выделением мишеней для иммунокоррекции препаратом на основе РНК двуспиральной натриевой соли (препарат РАДАМИН®ВИРО) с вторичным снижением риска COVID-19 в анализируемой группе.

Материалы и методы. Проведено двойное слепое плацебо контролируемое исследование терапевтических эффектов препарата на основе РНК двуспиральной натриевой соли в группе пациентов, контактировавших с лицами, имеющими подтверждённый диагноз COVID-19. Методом иммуноферментного анализа в динамике определяли в сыворотке крови и слюне содержание интерферона альфа и бета (IFNα и IFNβ соответственно), интерлейкина-1β и -10 (IL1β и IL-10 соответственно) у контактных лиц с ретроспективной оценкой изменения в зависимости от введения препарата или плацебо, а также развития COVID-19.

Результаты. В ходе представленного исследования продемонстрировано, что установленное содержание IFNα (менее 28 пг/мл) и IFNβ (менее 12 пг/мл) в слюне на 1–2 сут контакта выступает предиктором повышения риска развития COVID-19. При этом имеет значение степень увеличения данных иммунорегуляторных пептидов в интервале 2–3 дней контакта: IFNα и IFNβ на 250% и более позволяет нивелировать негативный прогноз у пациентов. Наиболее низкие показатели (p <0,001) INFα на 1–2 сут контакта, а также рост к 3 дню менее 21% наблюдались у лиц с окружностью талии более 80/94 см (женщины/мужчины). Заболеваемость в данной группе была выше и составила 85% (16 из 20 человек). Предикторной роли IL-1β и IL-10 в крови и слюне в отношении старта инфекционного процесса не выявлено. Введение препарата на основе РНК двуспиральной натриевой соли контактным пациентам позволило скорректировать интерфероновый ответ в виде повышения содержания IFNα и IFNβ, а также снизить заболеваемость в сравнении с группой плацебо.

Заключение. Отличия интерфероновой регуляции при контакте с SARS-CoV-2 в виде более низких уровней INF α и β, а также мало выраженная динамика роста в интервале первых 3-х дней влияли на повышение риска развития COVID-19. РАДАМИН®ВИРО может быть рекомендован в качестве средства постконтактной профилактики COVID-19 как для медицинских учреждений, так и у лиц, осуществляющих уход и/или контактировавших с больными COVID-19.

Ключевые слова: коронавирус; COVID-19; РНК двуспиральной натриевая соль; РАДАМИН®ВИРО; профилактика; индуктор интерферонов

Список сокращений: COVID-19 – инфекционное заболевание, вызываемое вирусом SARS-CoV-2; ЭАГ – эссенциальная артериальная гипертензия; ИИ – индуктор интерферонов; ОРЗ – острое респираторное заболевание; ПЦР – полимеразная цепная реакция; IWRS – система интерактивной интернет-рандомизации; э-ИРК – электронная индивидуальная регистрационная карта; IFNα – интерферон альфа; IFNβ – интерферон бета; IL1β – интерлейкин-1β; IL-10 – интерлейкин-10; МАНК – метод амплификации нуклеиновых кислот.

INTRODUCTION

In the context of the COVID-19 pandemic (the causative agent is the SARS-CoV-2 virus), taking into account the frequent occurrence of genovariants and their high contagiousness, the importance of preventive measures increases, and a post-exposure prophylaxis is a factor in preventing the spread of the disease. Drugs that can be used for this purpose should slow down the spread of the epidemic and/or pandemic and reduce the viral load on the body in the event of infection [1].

The course of a novel coronavirus infection has a variety of clinical manifestations: from severe pulmonary

ОРИГИНАЛЬНАЯ СТАТЬЯ
DOI: 10.19163/2307-9266-2023-11-2-137-148

lesions to a mild and/or asymptomatic course, which may be directly related to the individual response of the body to SARS-CoV-2, where regulatory peptides (cytokines) have a significant impact on the development and course of the diseases [2].

The interferon-mediated antiviral response has a direct relationship with a viral load, which depends on the infecting dose and the immune control degree of replication. The antiviral effects of the drug based on RNA double-stranded sodium salt are realized by stimulating the synthesis of type I interferons, as well as by changing the activity of the spectrum of toll-like receptors with a secondary immunomodulatory effect, which is realized through the links of both innate and adaptive immunity [3]. In the early stages of the infection, despite the inhibition of the endogenous HCoV IFN production, the use of an interferon inducer (II) based on RNA double-stranded sodium salt can act as a factor determining the control of the SARS-CoV-2 replication [4].

With regard to quarantine measures, their effect is not so high, because the data had been limited to case tracking and reporting, the isolation of critically ill patients in hospital, mild cases at home, and contact tracing. To reduce contact and transmission among the population, many countries have implemented social distancing but a high contribution of asymptomatic spread has shown the insufficiency of these measures [5, 6]. At the same time, the shortcomings of short-term measures have been noted; they are associated with the risk of a resumption of the rise in the incidence due to the late introduction of quarantine or its early cancellation [7, 8].

The studies have shown that the forecast for the spread of morbidity can be regarded as unfavorable. Global trends in globalization and urbanization reducing the effectiveness of administrative measures will not play a leading role and will not have a significant impact on the spread of epidemics and pandemics [9, 10].

Pharmaceutical companies around the world are searching for new highly effective innovative molecules characterized by both specific and nonspecific activities against pathogens of socially significant infectious diseases for a therapeutic and prophylactic use [11–13].

The COVID-19 pandemic has spurred the search for effective antivirals for both treatment and prevention of infectious diseases, and has shortened the timeline for introducing antivirals into treatment regimens. In the context of the pandemic, in clinical practice, the approval for the use of drugs for the treatment and prevention of COVID-19 was carried out according to an accelerated scheme for chemotherapeutic and biological drugs with constant and careful monitoring of their efficacy and safety [14, 15].

Currently, there are signs of the COVID-19 pandemic subsiding, which is a good opportunity to prepare effective therapeutic methods and replenish the “arsenal” with new effective and safe drugs [16].

It should be noted that even with a large coverage of the vaccinated and those who have already had COVID-19, the risk of the infection remains quite high, which is associated with the emergence of new SARS-CoV-2 sublines. One of such examples is the sub-variant of the SARS-CoV-2 virus (related to the XBB.1.16 line) – Arcturus, which has a greater virulence and resistance to the established immunity, as evidenced by a recently published study by Indian scientists [17].

With regard to preventive measures, it should be noted that a feature of the COVID-19 course is the presence of asymptomatic carriers and/or mild cases with symptoms of seasonal SARS, which, in turn, revealed the insufficiency of isolation and social distancing measures to control the pandemic [18, 19].

Taking into account the fact that families have members whose professional activities are associated with a continuous production and a constant contact with other people, the risk of infection of other family members increases significantly [20, 21].

As a prophylaxis, interferon therapy has an immunomodulatory and indirect antiviral effect upon contact with COVID-19 patients, contributing to the optimal response to the penetration of the virus and the production of intracellular antiviral proteins, which seems appropriate and justified for controlling the incidence in contact persons (family, work groups, mass gatherings of people, medical institutions) [22].

In the early stages of the infection, the use of II promotes the production of anti-inflammatory cytokines and, as a result, has a positive effect on reducing the risk of developing life-threatening conditions in patients [23].

Currently, in most industrialized countries including the Russian Federation, there is a constant search for effective molecules that have a direct and indirect effect on socially significant infectious diseases in order to prevent and treat them [24].

The results of a placebo-controlled study of RADAMIN®VIRO (RNA double-stranded sodium salt) prove its effectiveness in preventing a novel coronavirus infection. In case of COVID-19, the symptoms of the disease developed less frequently than in patients in the placebo group. A decrease in the frequency of development, duration and severity of the symptom complex characteristic of COVID-19 indicates a high efficiency of the drug. That actualizes the need to study the effect of drug based on RNA double-stranded sodium salt on the cytokine response (local and systemic) and the feasibility of its use for the purpose of immunocorrection in the context of therapy and prevention of respiratory viral infections, primarily COVID-19 [25].

THE AIM of the work was to study cytokine response characteristics in the group of persons

contacted by a novel coronavirus infection depending on the development of the disease over the next 14 days. Herewith, for the immunocorrection with a preparation based on RNA double-stranded sodium salt (RADAMIN®VIRO preparation) causing a secondary reduction in the risk of COVID-19 in the analyzed group, potential targets had been selected.

MATERIALS AND METHODS

Study design

Approval by the local ethics committee at National Research Ogarev Mordovia State University (protocol No. 5 dated May 17, 2020; approval dated April 30, 2022, protocol No. 105), a study of the local and systemic cytokine response of patients with an essential arterial hypertension (EAH) exposed to a novel coronavirus infection, was carried out. The features of the cytokine status associated with an increased risk of developing COVID-19 had been identified. The study was conducted from May 2020 to May 2022 based on the outpatient department of Republican Clinical Hospital No. 3, Saransk, Russia.

In the second part of the study (from June 1, 2022 to November 20, 2022), two groups were formed to investigate the immune effector of RNA double-stranded sodium salt. The 1st (placebo group) comprised 15 people aged 45 to 55 years, with EAH, who were in "close family contact" with COVID-19 patients. The 2nd (Test drug group) comprised 14 people aged 45 to 55 years with EAH who were in "close family contact" with COVID-19 patients. They were included in the study investigating the effects of the drug as a part of an additional study to the Clinical Study Protocol RAD-012022. The principle of a double-blind placebo-controlled study was the following: at the time of the administration and until the completion of the second stage of the study, neither the doctor nor the patient knew what therapy the subject was receiving, but the patient knew that he could receive RNA double-stranded sodium salt).

For dividing contact patients, two additional criteria were also introduced: a waist circumference (less than 80/94 cm (20 people) or more than 80/94 cm (15 people), women/men), and a retrospective criterion depending on the development of COVID-19 during 14 days of observation (sick and not sick).

The diagnosis of COVID-19 was established in accordance with the current Interim Guidelines for the Prevention, Diagnosis and Treatment of a Novel Coronavirus Infection.

Contact persons (in the placebo group) were administered a saline sodium chloride solution, 0.9%–5 ml once at the dose of 5 mg on the first day of treatment of an infected family member, which corresponded to 2 days of a direct contact. In group 1, material sampling (blood, saliva) was carried out three times: on the 1st–2nd days of contact with an infected patient, then on the 3rd and 7th days.

In the Radamin group, the participants were administered a drug based on RNA double-stranded sodium salt once at the dose of 5 mg on the 1st day of treatment of an infected family member, which corresponded to 2 days of a direct contact when compared with the main group. Before the administration of the drug based on RNA double-stranded sodium salt, on the 2nd day of contact with an infected patient, 1st day after the administration (corresponding to 3 days of contact with an infected patient), 3rd days after the administration (corresponding to 6–7 days of contact with an infected patient), blood and saliva were sampled.

The sampling of blood and unstimulated saliva for the both groups was carried out in the morning on an empty stomach (12 h without food and water). The blood was centrifuged (ARMED LC-04B centrifuge, Russia), followed by a serum separation and storage in labeled test tubes at -30°C for no more than 45 days. Before the saliva sampling, the participants rinsed their mouths with distilled water for 2 min immediately before sampling, and then saliva was collected for 15 minutes by passive salivation into graduated tubes. The levels of interferon alfa (IFNα) and interferon beta (INFβ), interleukin-1β and -10 (IL1β and IL-10, respectively) were determined by enzyme immunoassay (ELISA) in the laboratory of the Department of Immunology, Microbiology, Virology, National Research Ogarev Mordovia State University, on the enzyme immunoassay analyzer "Personal Lab TM" (Adaltis, Italy). The choice of the cytokines had been justified by the data of the previously conducted study and on the role of type I interferons. The ratio of pro- and anti-inflammatory cytokines in the antiviral immunity, as well as the results of a pilot study of the immune status of contact patients. The above studies were carried out before the start of this study and included 32 cytokines, the results were not published by the authors.

This study was conducted in accordance with the rules of Good Clinical Practice of the International Conference on Harmonization (ICH GCP), the ethical principles set forth in the Declaration of Helsinki of the World Medical Association (Fortaleza, 2013) and the requirements of the Russian legislation. A biological material (blood) was obtained for research taking into account the provisions of the WMA Declaration of Helsinki (2013) and the protocol of the Council of Europe Convention on Human Rights and Biomedicine (1999), taking into account the additional protocol to the Convention on Human Rights and Biomedicine in the field of biomedical research (2005).

Randomization of study subjects into groups

The subjects were randomized using an interactive online randomization system (Interactive Web

ОРИГИНАЛЬНАЯ СТАТЬЯ
DOI: 10.19163/2307-9266-2023-11-2-137-148

Randomization System, IWRS) embedded in an electronic individual registration card (eIRC). Before the start of the study, each investigator-physician who was delegated the responsibility of transferring the data to the eIRC was provided with an access code (a combination of a username and password) to the eIRC, as well as detailed written instructions for working with the eIRC, including the randomization procedure.

The randomization was carried out according to the following algorithm. Each subject that met all of the inclusion criteria and did not meet any of the exclusion criteria was assigned a three-digit randomization number by the IWRS system. The subject randomization number and other relevant data were entered by the investigator into the Subject Screening/Randomization Journal.

If a subject terminated the study participation prematurely, their randomization number was not reused and the subject was subsequently unable to participate further on.

Inclusion criteria

The inclusion criteria are as follows: the age from 45 to 55 years, the history of vaccination to prevent COVID-19 (no later than 6 months before the inclusion in the study), a presentation of the first infected family member on the 1st–2nd days when clinical symptoms of acute respiratory infections appear, a confirmation of the COVID-19 diagnosis in a family member by an express diagnostic method and then PCR, a consent of the contact person to sample their material for research on the 1st day of the infected family member's presentation, a consent of the contact person to participate in the study within 14 days with signing of a voluntary informed consent. For the main group, additionally, there should be a consent to the administration of a drug based on RNA double-stranded sodium salt, for the control group – placebo (physiological saline (NaCl) 0.9% – 5 ml.).

Non-inclusion criteria

They are associated clinical conditions in history: an acute cerebrovascular accident, myocardial infarction, angina pectoris, coronary revascularization, renal failure, type 1 diabetes mellitus, autoimmune, allergic diseases, the use of glucocorticosteroids, antiviral drugs and/or immunomodulators within 30 days before the inclusion in the study, a refusal of a patient to a long-term participation in the study.

Exclusion Criteria

A decision to exclude a subject from the study was made by the investigator. The subject was withdrawn from the study immediately if any of the following situations occurred:

1. The occurrence during the study course of any diseases or conditions that worsen the prognosis of the subject, and make it impossible for the subject to continue their participation in the clinical study.

If a subject was diagnosed with COVID-19 based on the results of SARS-CoV-2 RNA analyzes by the nucleic acid amplification test (NAAT), selected both at the screening stage and after it, and there was no need for hospitalization of the subject, he was not excluded from the study, he continued observation. If a subject needed to be hospitalized during the study course, he was excluded from the study.

2. Taking drugs of prohibited therapy or the need to be prescribed them.

3. Pregnancy (for study participants).

4. An invalid inclusion of a subject that does not meet the inclusion criteria and/or meets the non-inclusion criteria.

5. Other violations of the Protocol, which, in the opinion of the investigator, are significant.

6. A subject's refusal to participate in the study.

7. Other administrative reasons.

Statistical analysis

A statistical analysis was carried out using StatTech v. 2.8.8 (LLC "Stattech", Russia) and StatSoft Statistica 13.5. Quantitative indicators were assessed for the compliance with the normal distribution using the Shapiro-Wilk test (the number of patients in the group is fewer than 50). The data are presented as median (Me) and limits of 95% confidence interval (95% CI) or lower and upper quartiles (Q1–Q3). A comparison of two groups in terms of the quantitative indicator, the distribution of which differed from the normal one, was performed using the Mann-Whitney U-test for unrelated samples and the Wilcoxon test for dependent samples. The level of statistical significance for small samples (in this case, the effect of drug therapy on the risk of developing the disease) was calculated using the Fisher test (p <0.05).

To assess the diagnostic significance of quantitative signs in predicting a certain outcome, the method of analyzing ROC curves was used. The separating value of a quantitative trait at the cut-off point (the cut-off point was determined by the highest value of the Youden index) was calculated based on the specificity and sensitivity using the following formula: J=Sensitivity+Specificity–1 (where: J is the Youden index). The higher the specificity and sensitivity were, the higher the values of the Youden index were.

RESULTS

The persons who had been in the family contact with COVID-19 patients but did not subsequently become ill, had higher levels of INFα in the blood serum (more than 2.5 pg/ml) and saliva (more than 28 pg/ml); IFNβ in the blood serum (more than 3 pg/ml) and saliva (more than 12 pg/ml) at the time of the 1st–2nd days of contact. According to the obtained data, the threshold value of the INFα level in saliva on the 1st–2nd days of contact,

which corresponded to the highest value of the Youden index (0.79), was 14.5 pg/ml, indicating an increased risk of developing COVID-19 with a lower content of cytokine in saliva (the area under the ROC-curve was 0.917±0.055; 95% CI=0.810–1.000). The resulting model was statistically significant (p=0.004) and the level of INFα in saliva in the first days of contact had predictive information about the risk of developing COVID-19 in the exposed persons. The prediction of IFNα levels in the blood of the exposed persons on days 1–2 with respect to the changes in the risk of developing COVID-19 in the exposed persons was not detected (the resulting model was not statistically significant, $p > 0.05$).

For INFβ, the predictive value in relation to reducing the risk of developing COVID-19 in the exposed persons was its blood level of more than 2.7 pg/ml on days 1–2 (the area under the ROC-curve was 0.89±0.23; 95%, CI=0.76–0.93 The resulting model was statistically significant (p=0.0034) and in saliva, there was 13.5 pg/ml (the area under the ROC curve was 0.80±0.09; 95% CI=0.62–0.98 The resulting model was statistically significant (p=0.038).

When comparing the dynamic characteristics of the interferons contents (in the range between the 1st–2nd days and the 3rd one of contact with an infected patient) in the persons who had not fallen ill during 14 days of contact, an increase in INFα in saliva by 60–70% on day 3 was determined; it was significantly higher (p <0.001) than in the group of patients subsequently (10–23%).

The dynamics of the INFα contents in the same time period (between the 1st–2nd days and the 3rd one of contact with an infected patient) in the blood was not detected (p >0.05). The threshold value of the percentage increase in the level of INFα in saliva on the 3rd day of contact at the cut-off point which corresponded to the highest value of the Youden index (0.8), was 42%, which determined a decrease in the incidence of an acute disease when the percentage was above 42. The area under the ROC curve was 0.95 (95% CI: 0.87–1.000). The resulting model was statistically significant (p=0.002).

The data of the dynamic growth of the INFβ level in saliva and blood demonstrate significant differences in the groups: thus, the exposed persons (without COVID-19 in the next 14 days of the observation) were characterized by a threefold increase in the content of INFβ (p <0.001) by the 2nd day of contact which remained in saliva, and by 6–7 days of contact, but had leveled in the blood by days 6–7 (Tables 1, 2). On day 3, the threshold value of the percentage increase in the level of INFβ in saliva of the exposed persons at the cut-off point, which corresponded to the highest value of the Youden index (0.77), was 61%, which determined the decrease in the incidence of the acute disease when the percentage reached more than 61. The area under the ROC – curve was 0.96 (95% CI was 0.82–1.97). The resulting model was statistically significant (p=0.004).

It is important to note that on days 1–2 of contact, the lowest values (p <0.001) of the INFα levels were observed in the group of the individuals with a waist circumference of more than 80/94 cm (women/men) (in the blood 1.43 pg/ml, 95% CI [1.27–2.39] pg/ml, in saliva 11.7 pg/ml 95% CI [8.99–12.4] pg/ml), with a waist circumference of less than 80/94 cm (women / men): in the blood 2.57 pg/ml, 95% CI [1.48–2.97] pg/ml, in saliva 18.2 pg/ml 95% CI [15.1–41.7] pg/mL, and by day 3 of contact, the percentage of the increase was less than 21% [6–21]%. In this group of the exposed persons, the incidence was 85% (16 out of 20 people). The incidence among the persons with a waist circumference of less than 80/94 cm (women/men) was 30% (3 out of 15 people).

An increase in the IFNα and INFβ contents in the saliva and blood of the persons who had been in contact with a novel coronavirus infection in the absence of a disease in the next 14 days, was not accompanied by an increase in pro-inflammatory IL-1β. That significantly differed from the group of patients with a developed disease within 14 days of contact (p <0.001), but occurred against the background of an increase in anti-inflammatory IL-10 in saliva by days 6–7 of contact (Tables 1, 2).

The administration of the drug based on RNA double-stranded sodium salt intramuscularly at the dose of 5 mg once on days 1-2 to the contact patients with clinical manifestations of COVID-19, determined a decrease in the incidence in the next 14 days when compared with the placebo group. In the Test drug group, no sick persons were identified out of 14 patients, in the placebo group, 5 out of 15 contact persons which accounted for 30%, fell ill (Table 3).

Based on the data obtained, when analyzing the effect of the drug on the risk of developing the disease, statistically significant differences were revealed (p=0.042).

Taking into account the objective of the study, aimed at identifying the potential for correcting the interferon response with the administration of the drug RNA double-stranded sodium salt, the dynamics of changes in the content of IFNα and INFβ, IL-1β and IL-10 in saliva and blood serum against the background of the use of the drug was analyzed. At the time of the administration of RNA double-stranded sodium salt or placebo, the patients were characterized by comparable levels of IFNα and INFβ in the blood serum and saliva (p >0.05; Tables 4, 5). According to the previously reported data, they corresponded to an equal number of patients with IFNα and INFβ levels in saliva, to increase the risk of developing COVID-19 through contact with a SARS-CoV-2 infected person. 1 day after the administration of the drug, in serum and saliva of IFNα and INFβ in the form of the most pronounced increase in INFβ (Tables 4, 5), a statistically significant difference was noted between the Radamin and placebo groups.

ОРИГИНАЛЬНАЯ СТАТЬЯ
DOI: 10.19163/2307-9266-2023-11-2-137-148

Table 1 – Analysis of cytokine levels (pg/ml) in exposed persons blood on the novel coronavirus infection, depending on the development of the disease during the observation period

Indicators	Groups	Disease risk			*p*
		Me	Q_1–Q_3	*n*, persons	
INFα days 1–2 of contact	Not sick	2.61	2.23–3.01	32	0.030*
	Sick	2.15	1.67–2.29	35	
INFα day 3 of contact	Not sick	2.74	2.38–2.96	32	0.015*
	Sick	2.17	1.33–2.24	35	
INFα day 7 of contact	Not sick	2.74	2.33–3.62	32	0.001*
	Sick	2.08	1.64–2.35	35	
INFβ days 1–2 of contact	Not sick	3.51	3.12–4.92	32	0.019*
	Sick	1.82	1.08–2.84	35	
INFβ day 3 of contact	Not sick	13.3	6.17–15.8	32	<0.001*
	Sick	1.92	1.32–2.23	35	
INFβ day 7 of contact	Not sick	5.42	4.93–6.27	32	<0.001*
	Sick	2.35	1.28–3.17	35	
IL1β days 1–2 of contact	Not sick	4.51	4.26–5.39	32	0.204
	Sick	8.87	4.44–9.23	35	
IL1 β day 3 of contact	Not sick	5.09	4.51–7.10	35	0.015*
	Sick	21.5	14.50–24.78	32	
IL1 β day 7 of contact	Not sick	4.73	4.22–5.28	35	0.011*
	Sick	19.5	16.70–22.50	32	
IL-10 days 1–2 of contact	Not sick	9,72	9.05–10.39	35	0.06
	Sick	11.8	8.99–14.72	32	
IL-10 day 3 of contact	Not sick	10.6	8.96–11.30	35	0.07
	Sick	12.2	11.20–13.70	32	
IL-10 day 7 of contact	Not sick	10.1	9.43–11.27	35	0.394
	Sick	11.1	9.95–12.20	32	

Note: * – significant when comparing groups (“Sick” and “Not sick”) by the Mann-Whitney U-test.

Table 2 – Analysis of cytokines levels (pg/ml) in exposed persons’ saliva on the novel coronavirus infection, depending on the development of the disease during the observation period

Indicators	Groups	Cytokine level			*p*
		Me	Q_1–Q_3	*n*, persons	
INFα days 1–2 of contact	Not sick	38 I	28.7–42.1	32	0.003*
	Sick	12.7	9.13–14.5	35	
INFα day 3 of contact	Not sick	51.2	44.3–58.3	32	<0.001*
	Sick	14.5	8.23–18.7	35	
INFα day 7 of contact	Not sick	38.5	35.3–45.1	32	<0.001*
	Sick	15.6	7.91–19.5	35	
INFβ days 1–2 of contact	Not sick	17.23	9.54–22.7	32	0.035*
	Sick	4.34	3.48–4.92	35	
INFβ day 3 of contact	Not sick	51.8	47.5–60.4	32	<0.001*
	Sick	4.98	4.11–5.68	35	
INFβ day 7 of contact	Not sick	51.7	50.8–60.7	32	<0.001*
	Sick	18.7	17.7–24.1	35	
IL1 β days 1–2 of contact	Not sick	20.3	16.8–22.3	32	0.057
	Sick	29.50	26.50–31.6	35	
IL1 β day 3 of contact	Not sick	25.3	21.4–26.1	32	0.005*
	Sick	43.1	42.7–51.4	35	
IL1 β day 7 of contact	Not sick	19.5	18.4–20.1	32	<0.001*
	Sick	75.4	71.6–77.3	35	
IL-10 days 1–2 of contact	Not sick	26.8	23.4–33.5	32	0.63
	Sick	27.20	25.1–28.3	35	
IL-10 day 3 of contact	Not sick	27.12	21.7–32.5	32	0.75
	Sick	30.1	25.8–32.3	35	
IL-10 day 7 of contact	Not sick	43.7	40.6–60.5	32	0.019*
	Sick	31.8	27.6–35.1	35	

Note: * – significant when comparing groups (“Sick” and “Not sick”) by the Mann-Whitney U-test.

Table 3 – Analysis of the effect of therapy with drug based on RNA double-stranded sodium salt (compared with the placebo group) on the incidence of COVID-19 among the persons exposed to the novel coronavirus infection

Groups	Risk of disease		Risk of disease
	Not sick	Sick	
Radamin	14 (58.3)	0 (0.0)	0.042*
Placebo	10 (41.7)	5 (100.0)	

Note: * – differences in indicators are statistically significant (p <0.05; Fisher criterion).

Table 4 – Analysis of the cytokines levels (pg/ml) in the contact persons' saliva on the novel coronavirus infection, depending on the administration of drug based on RNA double-stranded sodium salt

Indicators	Groups	Levels			*p*
		Me	Q_1–Q_3	*n*, persons	
INFα before the administration	Radamin	33.5	11.8–41.7	14	0.760
	Placebo	35.4	12.1–40.3	15	
INFα in 1 day after the administration	Radamin	58.3	42.4–62.7	14	0.005*
	Placebo	41.4	11.7–48.3	15	
INFα in 3 days the administration	Radamin	41.7	34.5–49.1	14	0.026*
	Placebo	29.6	21.3–37.9	15	
INFβ before the administration	Radamin	8.30	3.65–18.5	14	0.247
	Placebo	16.6	8.04–19.9	15	
INFβ 1 day after the administration	Radamin	59.1	54.3–61.9	14	0.003*
	Placebo	52.7	7.26–54.1	15	
INF1b 3 days after the administration	Radamin	52.5	46.3–56.7	14	0.541
	Placebo	54.3	24.4–61.3	15	
IL1 β level before the administration)	Radamin	20 l	17.9–24.5	14	0.600
	Placebo	19.5	17.1–23.4	15	
IL1 β in 1 day after the administration	Radamin	24.6	22.4–28.8	14	0.965
	Placebo	23.7	22.2–35.4	15	
IL1 β in 3 days after the administration	Radamin	19.5	18.6–19.7	14	0.175
	Placebo	19.7	19.3–58.1	15	
IL-10 level before the administration	Radamin	27.6	24.5–33.3	14	0.585
	Placebo	27.2	24.7–32.6	15	
IL-10 in 1 day after the administration	Radamin	22.8	20.5–26.7	14	<0.001*
	Placebo	32.7	29.8–33.7	15	
IL-10 in 3 days after the administration	Radamin	41.2	39.1–43.5	14	0.064
	Placebo	62.4	38.3–68.1	15	
	Placebo	21.1	6.53–28.4	15	

Note: * – significant when comparing groups ("Sick" and "Not sick") by the Mann-Whitney U-test.

ОРИГИНАЛЬНАЯ СТАТЬЯ
DOI: 10.19163/2307-9266-2023-11-2-137-148

Table 5 – Analysis of the cytokines levels (pg/ml) in the blood of contact persons for a new coronavirus infection, depending on the administration of drug RNA double-stranded sodium salt

Indicators	Groups	Levels			*p*
		Me	Q_1–Q_3	*n*, persons	
INFα before the administration	Radamin	2.31	2,09–2,49	14	0,810
	Placebo	2.21	2,12–2,57	15	
INFα in 1 day after the administration	Radamin	2.71	2,47–3,08	14	0,043*
	Placebo	2.31	2,00–2,63	15	
INFα in 3 days after the administration	Radamin	2.98	2,45–3,91	14	0,041*
	Placebo	2.45	2,13–2,68	15	
INFβ before the administration	Radamin	2.95	1,61–4,66	14	0,371
	Placebo	4.15	2,51–4,97	15	
INFβ 1 day after the administration	Radamin	14.6	13,81–15,53	14	<0,001*
	Placebo	4.20	3,16–5,24	15	
INF1b 3 days after the administration	Radamin	5.55	4,84–6,27	14	0,071
	Placebo	4.44	3,41–5,47	15	
IL1 β level before the administration	Radamin	4.51	4,30–7,49	14	0,965
	Placebo	5.19	4,23–7,39	15	
IL1 β in 1 day after the administration	Radamin	5.97	4,78–9,23	14	0,485
	Placebo	4.75	4,13–12,9	15	
IL1 β in 3 days after the administration	Radamin	4.95	4,59–5,55	14	0,913
	Placebo	4.77	4,27–11,8	15	
IL-10 level before administration	Radamin	9,99	9,51–11,1	9	0,619
	Placebo	9,67	9,23–10,7	12	
IL-10 in 1 day after the administration	Radamin	10.8	10,4–11,4	12	0,488
	Placebo	9,51	9,03–11,6	12	
IL-10 in 3 days after the administration	Radamin	10.3	9,9–11,5	12	0,382
	Placebo	9,84	9,21–11,6	14	

Note: * – significant when comparing groups (“Sick” and “Not sick”) by the Mann-Whitney U-test.

According to the previously described data related to the group with an extremely high risk of developing the disease, when comparing individual indicators of changes in the content of interferons in the blood serum and saliva of contact persons, it was found out that in the patients (6 out of 14) with IFNα levels in the blood of less than 2.5 pg/ml and INFβ less than 3 pg/ml, and saliva less than 28 pg/ml, with the of the drug RNA double-stranded sodium salt, an increase in the concentration of these interferons by 2.5–3 times per day after the administration was noted. At the same time, it was also noted that these patients reached the indicators of individuals with a low risk of developing an acute disease. The analyzed 6 patients of this group were also characterized by a waist circumference of more than 80/94 cm (women/men). This trend in the form of a significant increase in the contents of IFNα and INFβ in individuals with comparable concentrations of interferons and waist circumferences above the norm was not registered with the administration of placebo.

DISCUSSION

In most cases, an immune response against human coronaviruses (HCoV), including a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [26, 27], is characterized by low levels of types I and III interferons (IFNs). This factor leads to an increase in the viral load followed by a hyperimmune response. The significance of the local and systemic interferon response is a significant factor both in the initiation of COVID-19 in contact persons and in the formation of clinical course features [28, 29].

In the course of the present study, it was demonstrated that the content of INFα in saliva less than 28 pg/ml and IFNβ less than 12 pg/ml on the 1st–2nd days of contact predicts an increased risk of developing COVID-19 in the persons who have been in contact with a novel coronavirus infection. However, in the interval of 2–3 days of contact, the degree of increase in these immunoregulatory peptides is also important, since an increase in IFNα and IFNβ by 250% or more makes it possible to level the negative prognosis in this category of patients.

It should be noted that the study was conducted during the period of dominance in the circulation of the Omicron virus variant, which, according to researchers, changes the synthesis of interferons to a lesser extent [28]. However, individually low IFNα and INFβ concentrations in saliva and blood, being a pathophysiological feature of patients, are primarily, with a waist circumference of more than 80/94 cm (women/men) and acting as a risk factor for developing COVID-19 in this category of patients upon the contact with a SARS-CoV-2 infected person, regardless of the virus associated with the variant, are able to suppress the data synthesis of immunoregulatory peptides.

Due to the high contagiousness of the novel variants of Omicron (Centaur, Cerberus, Kraken, Arcturus), the medical community attaches great importance to the search for the drugs that can correct the insufficient

(slow) interferon response in the patient at the time of the infection. The administration of the drug based on RNA double-stranded sodium salt (RADAMIN®VIRO) once intramuscularly at the dose of 5 mg determined the modification of both local and systemic interferon responses without a hyperactivation of the pro-inflammatory cytokine IL-1β. The most significant result of the use of the drug is an increase in the content of IFNα and INFβ in individuals with initially low levels, both in the blood and saliva, which, according to their own data, refers these patients to an increased risk of developing COVID-19 when they have a close family contact with an infected patient. In more cases, these patients were characterized by an increase in the waist circumference of more than 80/94 cm (women/men), which allows us to put forward a hypothesis about the additional significance of correcting the local and systemic interferon response in overweight and obese individuals who are in contact with a novel coronavirus infection. The use of a drug based on sodium ribonucleinate, reduces the risk of initiation and a complicated course of this infection.

The data of the present study indicate that the administration of the drug based on RNA double-stranded sodium salt did not reveal an average increase in the levels of anti-inflammatory cytokine (IL-10) in contact persons in the blood serum and saliva, which may depend on the multimodal effects of the drug, as well as on the characteristics of the individual immune response. A patient's status is realized through a protective and blocking effect on the reproduction of the virus in the incubation period, thereby leveling the pathophysiological need for the growth of IL-10.

CONCLUSION

The differences in the interferon regulation of the immune response upon a contact with SARS-CoV-2 in the form of lower INF α and β levels, as well as a slightly pronounced growth dynamics in the interval of the first 3 days, affected the increased risk of developing COVID-19, which had a pathogenetic justification. A clinically significant hypothesis put forward in the work is the association of a waist circumference of more than 80/94 cm with baseline low levels of type 1 interferons in the blood and saliva, which indicates a greater importance of correcting interferon synthesis in this category of patients. Undoubtedly, given the cascade type of work of the cytokine system, the revealed differences in the concentrations of pro-inflammatory IL-1β and anti-inflammatory IL-10 in the individuals with the development of an infectious process are of the fundamental importance, but these differences are secondary and reflect the onset of the disease in one of the groups. The levels of IL-1β and IL-10 at the time of the infection did not show a predictor role.

It is important to note that the IFN-mediated antiviral response depends on the viral load, which is the sum of the infecting dose and the degree of the immune control of replication. Interferonogen preparations have the potential to correct interferon synthesis, which is pathogenetically significant in the initiation and development of SARS-CoV-2 infection.

Despite the inhibition of endogenous IFN production, the use of an interferon inducer like RNA double-stranded sodium salt may be the factor determining the control of SARS-CoV-2 replication, especially in the early stages of the disease. It is important to note the safety of the drug, because the endogenous control mechanisms of the interferons contents in the body are preserved not higher than protective concentrations.

Thus, drug based on RNA double-stranded sodium salt can be recommended as a means of post-exposure COVID-19 prophylaxis, both for medical institutions (outpatient clinics and hospitals), and for those caring for and/or in contact with COVID-19 patients (including labor collectives and places of people's mass gathering). The use of RADAMIN®VIRO 5 mg (1 vial) intramuscularly once for the purpose of COVID-19 post-exposure prophylaxis significantly reduces the risk of contracting this disease, and has also a significant impact on reducing the burden of coronavirus infection in the socio-economic aspect of the fight against the pandemic.

FUNDING

The clinical study was carried out with the support of PROMOMED RUS LLC. The sponsor had no influence on the choice of material for publication, analysis and interpretation of the data.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHORS' CONTRIBUTION

Olga A. Radaeva – research conducting, text writing and editing; Larisa A. Balykova – study design implementation, study data processing; Kira Ya. Zaslavskaya – research design development, text editing; Yuliya A. Kostina – study design implementation, study data processing; Nikolai A. Pyataev – research data processing; Natalya M. Selezneva – study design implementation, study data processing; Alena V. Klimova – study design implementation, study results processing; Irina Y. Chegodaeva – study design implementation study design implementation, study data processing; Ksenia N. Koryanova – study data processing; Alexey V. Taganov – text editing, research data processing Petr A. Bely – study design implementation, study data processing.

All authors confirm that their authorship complies with the international ICMJE criteria (all authors have made a significant contribution to the development of the concept, research and preparation of the article, read and approved the final version before the publication).

ОРИГИНАЛЬНАЯ СТАТЬЯ
DOI: 10.19163/2307-9266-2023-11-2-137-148

REFERENCES

1. Mordyk AV, Saifulina ML, Bagisheva NV, Antipova EP. Prevention of COVID-19 in family foci. Lechaschi Vrach. 2021;(2):61–3. DOI: 10.26295/OS.2021.92.25.012. Russian
2. Smirnov VS, Leneva IA, Kudryavtseva TA, Fayzuloev EB, Zaplutanov VA, Petlenko SV, Kartashova NP, Gracheva AV, Korchevaya ER. Possibilities of suppressing the cytopathogenic effect of SARS-CoV-2 coronavirus according to the results of the antiviral activity of Cytovir®-3 *in vitro* study. Antibiotics and Chemotherapy. 2021;66(5–6):4–10. DOI: 10.37489/0235-2990-2021-66-5-6-4-10. Russian
3. Sokolova TM, Shuvalov AN, Poloskov VV, Shapoval IM, Kostinov MP. Stimulation of signal receptor gene expression and induction of cytokine synthesis in human blood cells under the action of sodium ribonucleate and its combinations with influenza vaccines in vitro. Molecular Medicine. 2015;(1):12–7. Russian
4. Narovlyansky AN, Ershov FI, Sanin AV, Pronin AV. Interferon system for COVID-19. Immunologiya. 2022;43(3):245–54. DOI: 10.33029/0206-4952-2022-43-3-245-254. Russian
5. Fedenok JN, Burkova VN. Social distancing as altruism in the context of the coronavirus pandemic: a cross-cultural study. Siberian historical research. 2020;(2): 6–40. DOI: 10.17223/2312461X/28/1
6. Tindale LC, Stockdale JE, Coombe M, Garlock ES, Lau WYV, Saraswat M, Zhang L, Chen D, Wallinga J, Colijn C. Evidence for transmission of COVID-19 prior to symptom onset. Elife. 2020 Jun 22;9:e57149. DOI: 10.7554/eLife.57149
7. Zhang J, Litvinova M, Wang W, Wang Y, Deng X, Chen X, Li M, Zheng W, Yi L, Chen X, Wu Q, Liang Y, Wang X, Yang J, Sun K, Longini IM Jr, Halloran ME, Wu P, Cowling BJ, Merler S, Viboud C, Vespignani A, Ajelli M, Yu H. Evolving epidemiology and transmission dynamics of coronavirus disease 2019 outside Hubei province, China: a descriptive and modelling study. Lancet Infect Dis. 2020 Jul;20(7):793–802. DOI: 10.1016/S1473-3099(20)30230-9
8. Fraser C, Riley S, Anderson RM, Ferguson NM. Factors that make an infectious disease outbreak controllable. Proc Natl Acad Sci U S A. 2004 Apr 20;101(16):6146–51. DOI: 10.1073/pnas.0307506101
9. Hellewell J, Abbott S, Gimma A, Bosse NI, Jarvis CI, Russell TW, Munday JD, Kucharski AJ, Edmunds WJ; Centre for the Mathematical Modelling of Infectious Diseases COVID-19 Working Group; Funk S, Eggo RM. Feasibility of controlling COVID-19 outbreaks by isolation of cases and contacts. Lancet Glob Health. 2020 Apr;8(4):e488–e496. DOI: 10.1016/S2214-109X(20)30074-7. Epub 2020 Feb 28. Erratum in: Lancet Glob Health. 2020.
10. Briko NI, Kagramanyan IN, Nikiforov VV, Suranova TG, Chernyavskaya OP, Polezhaeva NA. Pandemic COVID-19. Prevention Measures in the Russian Federation. Epidemiology and Vaccinal Prevention. 2020;19(2):4-12. DOI: 10.31631/2073-3046-2020-19-2-4-12. Russian
11. Andrew DP, Chang MS, McNinch J, Wathen ST, Rihanek M, Tseng J, Spellberg JP, Elias CG 3rd. STCP-1 (MDC) CC chemokine acts specifically on chronically activated Th2 lymphocytes and is produced by monocytes on stimulation with Th2 cytokines IL-4 and IL-13. J Immunol. 1998 Nov 1;161(9):5027–38.
12. Beeching NJ, Fletcher TE, Fowler R. Coronavirus Disease (COVID-19). BMJ Best Practices. Available from: https://bestpractice.bmj.com/topics/en-us/3000168.
13. Li R, Pei S, Chen B, Song Y, Zhang T, Yang W, Shaman J. Substantial undocumented infection facilitates the rapid dissemination of novel coronavirus (SARS-CoV-2). Science. 2020 May 1;368(6490):489–93. DOI: 10.1126/science.abb3221
14. Baklaushev VP, Kulemzin SV, Gorchakov AA, Lesnyak VN, Yusubalieva GM, Sotnikova AG. COVID-19. Aetiology, pathogenesis, diagnosis and treatment. Journal of Clinical Practice. 2020;11(1):7-20. DOI: 10.17816/clinpract26339
15. Samoilova AV. The role of Roszdravnadzor in ensuring quality and safe medical care during the spread of a new coronavirus infection (COVID-19). National Health Care (Russia). 2020;1(1):16-22. Russian
16. Soldatov AA, Avdeeva ZhI, Gorenkov DV, Khantimirova LM, Paramonova YuS, Smolina EM, Bondarev VP, Merkulov VA. The efficacy of medicinal products based on plasma immunoglobulins and monoclonal antibodies for the treatment and prevention of COVID-19. Immunologiya. 2022;43(5):485–503. DOI: 10.33029/0206-4952-2022-43-5-485-503. Russian
17. Kim K, Cho K, Song J, Rahmati M, Koyanagi A, Lee SW, Yon DK, Il Shin J, Smith L. The case fatality rate of COVID-19 during the Delta and the Omicron epidemic phase: A meta-analysis. J Med Virol. 2023 Feb;95(2):e28522. DOI: 10.1002/jmv.28522
18. Tamm MV. COVID-19 in Moscow: prognoses and scenarios. FARMAKOEKONOMIKA. Modern Pharmacoeconomics and Pharmacoepidemiology. 2020;13(1):43–51. DOI: 10.17749/2070-4909.2020.13.1.43-51. Russian
19. Gipaeva GA. COVID-19 prevention and its effectiveness: reference review. In: Sorokin EL, editor. Science and society: materials of the XV All-Russian scientific and practical conference; 2020 Dec 2 2020; Novosibirsk: Publishing House of ANO DPO “SIPPPISR”; 2020. P. 44–50. DOI: 10.38163/978-5-6043859-4-4_2020_44. Russian
20. Tay MZ, Poh CM, Rénia L, MacAry PA, Ng LFP. The trinity of COVID-19: immunity, inflammation and intervention. Nat Rev Immunol. 2020 Jun;20(6):363-374. DOI: 10.1038/s41577-020-0311-8
21. Abakushina EV. Immunological aspects of coronavirus disease caused by SARS-CoV-2. Genes & Cells. 2020;15(3):14–21. DOI: 10.23868/202011002
22. Usenko DV. Prospects for finding means of non-specific prevention of COVID-19 infection. Meditsinskiy sovet=Medical Council. 2022;(6):36–42. DOI: 10.21518/2079-701X-2022-16-6-36-42. Russian
23. Radaeva OA, Taganov AV, Rogozhina EA. Prospects of using interferon inducers of the double stranded RNA type for the treatment of viral and bacterial infections. Russian Medical Inquiry. 2022;6(11):643–9. DOI: 10.32364/2587-6821-2022-6-11-643-649. Russian
24. Andrew DP, Chang MS, McNinch J, Wathen ST, Rihanek M, Tseng J, Spellberg JP, Elias CG 3rd. STCP-1 (MDC) CC chemokine acts specifically on chronically activated Th2 lymphocytes and is produced by monocytes on stimulation with Th2 cytokines IL-4 and IL-13. J Immunol. 1998 Nov 1;161(9):5027–38.
25. Balykova LA, Radaeva OA, Zaslavskaya KY, Taganov AV, Bely PA, Zakharov KA, Popova VV, Chudinovskikh TI, Teplykh SV, Balaban IV, Kozlov RS, Kirichenko NV, Simakina EN, Koryanova KN, Pushkar DYu. Post-exposure

prophylaxis of COVID-19: results of double-blind, placebo-controlled, multicenter clinical study evaluation of efficacy and safety of double-stranded sodium salt RNA drug. Pharmacy & Pharmacology. 2023;11(1):72–88. DOI: 10.19163/2307-9266-2023-11-1-72-88

26. Hadjadj J, Yatim N, Barnabei L, Corneau A, Boussier J, Smith N, Péré H, Charbit B, Bondet V, Chenevier-Gobeaux C, Breillat P, Carlier N, Gauzit R, Morbieu C, Pène F, Marin N, Roche N, Szwebel TA, Merkling SH, Treluyer JM, Veyer D, Mouthon L, Blanc C, Tharaux PL, Rozenberg F, Fischer A, Duffy D, Rieux-Laucat F, Kernéis S, Terrier B. Impaired type I interferon activity and inflammatory responses in severe COVID-19 patients. Science. 2020 Aug 7;369(6504):718–24. DOI: 10.1126/science.abc6027

27. Jamilloux Y, Henry T, Belot A, Viel S, Fauter M, El Jammal T, Walzer T, François B, Sève P. Should we stimulate or suppress immune responses in COVID-19? Cytokine and anti-cytokine interventions. Autoimmun Rev. 2020 Jul;19(7):102567. DOI: 10.1016/j.autrev.2020.102567

28. Laine L, Skön M, Väisänen E, Julkunen I, Österlund P. SARS-CoV-2 variants Alpha, Beta, Delta and Omicron show a slower host cell interferon response compared to an early pandemic variant. Front Immunol. 2022 Sep 30;13:1016108. DOI: 10.3389/fimmu.2022.1016108

29. Park A, Iwasaki A. Type I and Type III Interferons – Induction, Signaling, Evasion, and Application to Combat COVID-19. Cell Host Microbe. 2020 Jun 10;27(6):870–8. DOI: 10.1016/j.chom.2020.05.008

30. Bakadia BM, He F, Souho T, Lamboni L, Ullah MW, Boni BO, Ahmed AAQ, Mukole BM, Yang G. Prevention and treatment of COVID-19: Focus on interferons, chloroquine/hydroxychloroquine, azithromycin, and vaccine. Biomed Pharmacother. 2021 Jan;133:111008. DOI: 10.1016/j.biopha.2020.111008

AUTHORS

Olga A. Radaeva – Doctor of Sciences (Medicine), Associate Professor, Head of the Department of Immunology, Microbiology and Virology with a Course of Clinical Immunology and Allergology, National Research Ogarev Mordovia State University. ORCID ID: 0000-0003-1383-2474. E-mail: radaevamed@mail.ru

Larisa A. Balykova – Doctor of Sciences (Medicine), Professor, Corresponding Member of the Russian Academy of Sciences, Head of the Department of Pediatrics, Director of Medical Institute, National Research Ogarev Mordovia State University. ORCID ID: 0000-0002-2290-0013. E-mail: larisabalykova@yandex.ru

Kira Ya. Zaslavskaya – Assistant of the Department of Biological and Pharmaceutical Chemistry with a Course of Organization and Management of Pharmacy, National Research Ogarev Mordovia State University. ORCID ID: 0000-0002-7348-9412. E-mail: kiryonok@yandex.ru

Yuliya A. Kostina – Candidate of Sciences (Medicine), Associate Professor of the Department of Immunology, Microbiology and Virology with a Course in Clinical Immunology and Allergology, National Research Ogarev Mordovia State University. ORCID ID: 0000-0002-7825-7856. E-mail: bazunova.2013@mail.ru

Nikolai A. Pyataev – Doctor of Sciences (Medicine), Associate Professor, Head of the Department of Anesthesiology and Intensive Care, National Research Ogarev Mordovia State University. ORCID ID: 0000-0002-9688-7640. E-mail: pyataevna@mail.r

Natalya M. Selezneva – Candidate of Sciences (Medicine), Associate Professor of the Department of Hospital Therapy, National Research Ogarev Mordovia State University. ORCID ID: 0000-0002-3004-2063. E-mail: nata_rm@mail.ru

Alena V. Klimova – PhD student of the Department of Immunology, Microbiology and Virology with a course of Clinical Immunology and Allergology, National Research Ogarev Mordovia State University. ORCID ID: 0009-0001-9356-6745. E-mail: alyonka-class@mail.ru

Irina Y. Chegodaeva – 6th year student of the specialty of "Pediatrics" of National Research Ogarev Mordovia State University. ORCID ID: 0000-0001-7973-5015. E-mail: Chegodaeva-irina@ro.ru

Ksenia N. Koryanova – Candidate of Sciences (Pharmacy), Associate Professor of the Department of Pharmacology with a Course of Clinical Pharmacology, Pyatigorsk Medical and Pharmaceutical Institute – branch of Volgograd State Medical University. ORCID ID: 0000-0003-1571-9301. E-mail: kskor-16@mail.ru

Alexey V. Taganov – Doctor of Sciences (Medicine), Professor of the Department of Dermatovenereology with a Cosmetology Course of the Faculty of Continuous Medical Education of the Medical Institute of Peoples' Friendship University of Russia. ORCID ID: 0000-0001-5056-374X. E-mail: matis87177@yandex.ru

Petr A. Bely – Candidate of Sciences (Medicine), Senior Laboratory Assistant, Department of Propaedeutics of Internal Diseases and Gastroenterology, Moscow State Medical and Dental University n.a. A.I. Evdokimov. ORCID ID: 0000-0001-5998-4874. E-mail: pbely@ncpharm.ru