DOI: https://doi.org/10.17816/brmma71302

DYNAMICS OF ENDOGENOUS INTERFERON-ALPHA AND -GAMMA PRODUCTION UNDER THE INFLUENCE OF INGARON THERAPY IN PATIENTS WITH CHRONIC EPSTEIN – BARR VIRAL INFECTION WITH CHRONIC FATIGUE SYNDROME

I.A. Rakityanskaya[1], T.S. Ryabova[1, 2], A.A. Kalashnikova[3], A.S. Manuilov[2], A.N. Bel'skikh[2], A.V. Apchel[4]

[1] City Ambulant Department № 112, Saint Petersburg, Russia

[2] Military Medical Academy named after S.M. Kirov of the Ministry of Defense of the Russian Federation, Saint Petersburg, Russia

[3] All-Russian Center for Emergency and Radiation Medicine named after A.M. Nikiforov, Saint Petersburg, Russia

[4] Severo-Western Medical Training Center for Postgraduate Education, Saint Petersburg, Russia

***ABSTRACT*:** The influence of antiviral therapy with ingaron on the dynamics of production of interferons α and γ and clinical effects in patients with chronic viral Epstein – Barr infection was studied. The study involved 51 patients (33 women and 17 men aged 35,27 ± 1,28 years) suffering from chronic infection caused by the Epstein – Barr virus. The duration of the disease from the appearance of the first complaints to laboratory confirmation of the Epstein – Barr virus infection and diagnosis was 2,23 ± 0,21 years. Determined the serum, spontaneous and induced production of cytokines interferons α and γ in serum and in the culture of lymphocytes. Three months after the end of antiviral therapy, in patients with an initially low level of induced interferon-γ, the production of interferon-γ increased. The absence of an increase in the production of induced interferon-γ in patients one and three months after the end of therapy with ingaron indicates the absence of the effect of the drug on the level of endogenous interferon-γ. It has been established that the initially low level of induced interferon-γ can be a marker of the positive effect of the therapy with ingaron. Correlation analysis revealed the effect of baseline interferon-γ induced on the clinical picture of the disease. Thus, initially a high level of induced interferon-γ (2706 ± 1058.94 pg/ml) inversely affects the development of sweating in patients (r = –0.506, p = 0,023; τ = –0.419, p = 0.021), and initially low level of the induced IFN-γ (287.2 ± 64.65 pg/ml) — on development of weakness (r = –0.405, p = 0.045; τ = –0.419, p = 0.037). In general, ingarone can be used in the therapy of patients with chronic Epstein virus — Bar infection at a dose of 500,000 IU every other day, at least 10 injections.

Keywords: acyclic nucleosides; interferon γ and α; the number of copies of deoxyribonucleic acid; complex antiviral therapy; chronic fatigue syndrome; T-cell immunity; chronic infection caused by the Epstein–Barr virus.

To cite this article:
Rakityanskaya IA, Ryabova TS, Kalashnikova AA, Manuilov AS, Bel'skikh AN, Apchel AV. Dynamics of endogenous interferon-alpha and -gamma production under the influence of ingaron therapy in patients with chronic Epstein – Barr viral infection with chronic fatigue syndrome. *Bulletin of the Russian Military Medical Academy*. 2021;23(2):17–28. DOI: https://doi.org/10.17816/brmma71302

Received: 04.05.2021 **Accepted:** 25.05.2021 **Published:** 20.06.2021

УДК 616.615.036; 578.825.13
DOI: https://doi.org/10.17816/brmma71302

ДИНАМИКА ПРОДУКЦИИ ЭНДОГЕННОГО ИНТЕРФЕРОН-АЛЬФА И -ГАММА ПОД ВЛИЯНИЕМ ТЕРАПИИ ИНГАРОНОМ У БОЛЬНЫХ ХРОНИЧЕСКОЙ ЭПШТЕЙНА – БАРР ВИРУСНОЙ ИНФЕКЦИЕЙ С СИНДРОМОМ ХРОНИЧЕСКОЙ УСТАЛОСТИ

И.А. Ракитянская[1], Т.С. Рябова[1, 2], А.А. Калашникова[3], А.С. Мануилов[2], А.Н. Бельских[2], А.В. Апчел[4]

[1] Городская поликлиника № 112, Санкт-Петербург, Россия

[2] Военно-медицинская академия имени С.М. Кирова МО РФ, Санкт-Петербург, Россия

[3] Всероссийский центр экстренной и радиационной медицины имени А.М. Никифорова, Санкт-Петербург, Россия

[4] Северо-Западный медицинский учебный центр последипломного образования, Санкт-Петербург, Россия

Резюме. Изучено влияние противовирусной терапии ингароном на динамику продукции интерферонов α и γ и клинические эффекты у больных хронической вируснойинфекцией Эпштейна – Барр. Обследован 51 пациент (33 женщины и 17 мужчин в возрасте 35,27 ± 1,28 лет), страдающих хронической инфекцией, вызванной вирусом Эпштейна – Барр. Длительность заболевания от появления первых жалоб до лабораторного подтверждения вирусной инфекцией Эпштейна – Барр и постановки диагноза составила 2,23 ± 0,21 года. Определяли сывороточную, спонтанную и индуцированную продукцию цитокинов интерферонов α и γ в сыворотке и в культуре лимфоцитов. Через три месяца после окончания противовирусной терапии у больных с исходно низким уровнем индуцированного интерферона-γ продукция интерферона-γ увеличилась. Отсутствие увеличения продукции индуцированного интерферона-γ у больных через один и три месяца после окончания терапии ингароном свидетельствует об отсутствии влияния препарата на уровень эндогенного интерферона-γ. Установлено, что исходно низкий уровень индуцированного интерферона-γ может быть маркером положительного эффекта проводимой терапии ингароном. Корреляционный анализ позволил выявить влияние исходного уровня индуцированного интерферона-γ на клиническую картину заболевания. Так, исходно высокий уровень индуцированного интерферона-γ (2706 ± 1058,94 пг/мл) обратно влияет на развитие у больных потливости (r = –0,506, p = 0,023; τ = –0,419, p = 0,021), а исходно низкий уровень индуцированного интерферона-γ (287,2 ± 64,65 пг/мл) — на развитие слабости (r = –0,405, p = 0,045; τ = –0,419, p = 0,037). В целом ингарон может быть использован в терапии больных хронической вирусной инфекцией Эпштейна – Барр в дозе 500 000 МЕ через день, не менее 10 инъекций.

Ключевые слова: ациклические нуклеозиды; интерферон γ и α; количество копий дезоксирибонуклеиновой кислоты; комплексная противовирусная терапия; синдром хронической усталости; Т-клеточный иммунитет; хроническая инфекция, вызванная вирусом Эпштейна – Барр.

Как цитировать:
Ракитянская И.А., Рябова Т.С., Калашникова А.А., Мануилов А.С., Бельских А.Н., Апчел А.В. Динамика продукции эндогенного интерферон-альфа и -гамма под влиянием терапии ингароном у больных хронической Эпштейна – Барр вирусной инфекцией с синдромом хронической усталости // Вестник Российской военно-медицинской академии. 2021. Т. 23, № 2. С. 17–28. DOI: https://doi.org/10.17816/brmma71302

Рукопись получена: 04.05.2021 **Рукопись одобрена:** 25.05.2021 **Опубликована:** 20.06.2021

Interferons (IFN) are essential biological regulatory proteins (cytokines) and are mediators of cellular homeostatic reactions. They are produced in response to a viral infection and inhibit the replication of a wide range of deoxyribonucleic (DNA) and ribonucleic (RNA) acid viruses, which are implemented through viral polypeptide synthesis [1]. With the administration of IFN in vivo, the level of viremia decreases, i.e., they can be used as antiviral drugs. The antiviral effect is mediated both by the immune system and by intracellular antiviral mechanisms. According to the amino acid sequence, IFNs are divided into three classes, called types I, II, and III IFNs [2].

Type II IFN, or immune IFN-γ, is a highly pleiotropic cytokine secreted not in response to viral infection but indirectly by mitogen-activated T cells and natural killer (NK) cells, which are the primary producers of IFN-γ during the innate and adaptive phases of the immune response to viral infection. IFN-γ is significant in the activation of macrophages for the production of tumor necrosis factor-α (TNF-α), increases macrophage phagocytosis and microbicidal activity, the formation of active nitrogen and oxygen intermediates, including superoxide radicals, nitric oxide, and hydrogen peroxide, as well as stimulates Th1-T cell response and has robust inflammatory activity. IFN-γ increases the count of lymphocytes and leads to their long-term persistence in the tissue, induces the activation of the cascade of complement components and an acute phase response, plays a role in the changeover of the production of the immunoglobulin (Ig) G class, and has a direct antiviral effect [3]. Usually, in the early stages of the host immune response, the production of IFN-γ by NK cells, $CD4^+$ T cells (Th1), and $CD8^+$ T cells is aimed at improving antigen recognition in antigen-presenting cells. IFN-γ is one of the critical cytokines differentiating native CD4 cells into effector Th1 T cells that produce the primary mediators of cellular immunity against viral and intracellular bacterial infections [4]. IFN-γ and interleukin (IL) 12 generate a robust Th1 response, which affects the differentiation of naive T cells into Th1 or Th2 cells. When activated, almost all $CD8^+$ T cells, NK cells, and Th1 lymphocytes produce IFN-γ, which stimulates cytokine activity and increases the expansion of NK cells. IFN-γ increases antigen presentation of the major histocompatibility complex (HLA) class I and II by increasing the expression and activity of proteasomes, resulting in increased host sensitivity to the pathogen and ability to identify and respond to this pathogen [5]. Thus, IFN-γ has many important immunostimulatory and immunomodulatory effects.

When infected with a virus, IFN-γ can induce apoptosis by regulating Fas ligand to remove virus-infected cells, enhances the expression of type I IFN, proinflammatory cytokines and chemokines by endothelial and epithelial cells, and fibroblasts to attract macrophages, neutrophils, and T cells to the sites of infection [6]. IFN-γ can also initiate the expression of dsRNA-specific adenosine deaminase (ADAR), which inhibits viral replication by editing or disrupting the translation of viral proteins [7]. IFN-γ is a potent antiviral cytokine that interferes with various stages of the virus life cycle in stimulated cells using the following mechanisms. It inhibits viral entry at both the extracellular and intracellular stages; blocks replication by disrupting the replication niche; disrupts gene expression by interfering with translation and assembly of the nucleocapsid; impairs the virus isolation by breaking the disulfide bond of the necessary participant in the cellular interaction; alters reactivation by suppressing the primary regulator of viral transcription. IFN-γ can also inhibit viral entry at the stage of transfer of the invading virus from the endosome to the cytoplasm [8].

In recent years, numerous works have been published worldwide on treating herpesvirus infections with recombinant IFN-γ, which show high clinical and antiviral efficacy [9–14]. It has been revealed that IFN-γ has a 7–10 times more potent antiviral effect than IFN-α or -β. Epstein–Barr virus (EBV)-induced B cell proliferation and immunoglobulin secretion are reduced when IFN-γ is administered 3–4 days after infection. At the same time, the addition of IFN-α and IFN-β only has an effect for 24 hours. The authors of the work suggested that, at an early stage, EBV-infected cells can be regulated by all IFNs. There is an intermediate period when only IFN-γ can directly influence the EBV-induced reactions of B cells. In phase 3, B-lymphocytes become insensitive to the direct action of all IFNs and are affected only by cytotoxic cells [15]. In 2002, high efficiency of inhibition of replication of herpes simplex virus type 1 (HSV-1) by administration of recombinant IFN-γ was revealed, resulting from a synergistic interaction with endogenous IFN-α/β, which is locally produced in response to HSV-1 infection [16]. A double-blind, placebo-controlled study showed that subcutaneous administration of recombinant IFN-γ 3 times a week reduces the incidence of severe infections in patients suffering from various genetic types of chronic granulomatous disease [17].

In the Russian Federation, the only IFN-γ agent under the trade name Ingaron was registered, developed by the company NPP PHARMAKLON by the microbiological synthesis in a recombinant E. Coli strain purified by column chromatography. The agent consists of 144 amino acid residues, devoid of the first three, Cys-Tyr-Cys, replaced by Met.

Previously, we [18] published the results of studying the efficiency of Ingaron therapy one month after the end of therapy on the dynamics of INF-α and -γ levels (spontaneous, serum, and induced) in patients with chronic EBV infection (CEBVI).

The study aimed to analyze the effect of Ingaron 1 and 3 months after the end of therapy on the dynamics of INF-α and -γ production (spontaneous, serum, and induced levels) and the clinical presentation in CEBVI patients with the development of chronic fatigue syndrome 1 and 3 months after the end of therapy.

DOI: https://doi.org/10.17816/brmma71302

MATERIALS AND METHODS

The study included 33 female and 17 male CEBVI patients aged 35.27 ± 1.28 years. The duration of CEBVI from the first complaints to laboratory confirmation of EBV infection and diagnosis establishment was 2.23 ± 0.21 years. In 38 (74.5%) patients had chronic tonsillitis often aggravated in childhood and not amenable to antibiotic therapy, and 13 (25.49%) patients had a history of infectious mononucleosis. All patients underwent differential diagnostics of CEBVI with other viral infections (human immunodeficiency virus, viral hepatitis, cytomegalovirus infection, and toxoplasmosis), helminthic invasions, and autoimmune diseases associated with EBV infection. The patients were diagnosed with chronic fatigue syndrome (CFS) based on the clinical and laboratory study, according to the diagnostic criteria published by the Centers for Disease Control (CDC, United States of America) in 1988, 1991, 1992, and 1994. This disease was first reported by American doctors P. Cheney and D. Peterson in 1984, and in 1988, CFS was identified as an independent disease [19]. In 1994, the CDC revised the reported cases of CFS and developed diagnostic criteria for this disease [20]. In 2000, the American College of Rheumatology developed and approved an extended and updated version of the uniform diagnostic criteria for CFS [21]. CFS represents a complex chronic disease characterized by intense, unmotivated general asthenia (physical and mental) that interferes with daily activities, is not eliminated after rest, worsens with physical exertion, and is associated with somatic, neurological, mental, and unspecified general disorders [22]. CEBVI associated with CFS is characterized by a prolonged course and frequent relapses with clinical and laboratory signs of viral activity, which are described in detail in the literature [23, 24].

Patients suffer from prolonged low-grade fever (37.1–37.3 °C), asthenia, unmotivated fatigue, excessive hyperhidrosis (especially at night), a constant feeling of discomfort and/or pain in the throat, lymphadenitis, swelling of the nasal mucosa with a profuse drip of mucus, and stomatitis. Some patients develop a cough, skin rashes, arthralgia, and pain in the muscles of the trunk and extremities are possible. There may be manifestations of conjunctivitis and otitis. Neurological disorders often develop, including headaches, memory and sleep disturbances, decreased concentration, irritability, tearfulness, and a tendency to depression. An increase in internal organs (hepato- or splenomegaly, according to ultrasound) and intensifying feelings of heaviness in the right hypochondrium are possible. Also, patients complain of frequent cold-related diseases and the addition of other herpes virus infections. In the clinical blood analysis, relative and absolute lymphocytosis, monocytosis, and neutropenia are noted; less often, there may be lymphopenia and leukopenia. In anamnesis, such patients often have long-term stressful situations and psychoemotional and physical overload against which the patient's condition deteriorates.

Clinical research methods included the collection of anamnesis, data on previous immuno- or antiviral therapy, and the presence of concomitant diseases. The clinical condition of patients was assessed according to the generally accepted method, including objective data and registration of patient complaints at the time of examination. The severity of the patient's complaints was recorded using a subjective assessment scale on a 3-point scale (0 — no symptoms, 1 — mild symptoms, 2 — moderate symptoms, 3 — severe symptoms).

Diagnostics of CEBVI were based on clinical data and positive results of EBV DNA studies in saliva samples by polymerase chain reaction (PCR) with real-time hybridization-fluorescence detection. Test systems AmpliSense EBV/CMV/HHV6-screen-FL of the Central Research Institute of Epidemiology (Russia) were used. The units of measurement used to assess the viral load during DNA extraction from saliva were the number of copies of EBV DNA per 1 ml of sample (NCDNA). According to the instructions, this indicator is calculated by the equation NCDNA = DNAC × 100, where DNAC is the number of copies of virus DNA in the sample. The analytical sensitivity of the test system is 400 copies/ml.

EBV is known to be spread by contact with saliva and penetrates through the epithelium that lines the nasopharynx. The lymphoid system surrounding the nasopharyngeal region includes the adenoids and tonsils and is called the Waldeyer's ring. The level of infected B cells in the population varies from 5 to 3000 for every 10^7 memory B cells in both the peripheral blood (average $110/10^7$) and the Waldeyer's ring (average $175/10^7$), i.e., the virus is uniformly distributed throughout the ring [25]. Thus, the level of infected cells is similar between the peripheral blood and the Waldeyer's ring, and only 1% of these cells are detected in the peripheral blood. The virus constantly leaks into the oral cavity, where it mixes with saliva for about 2 minutes before each act of swallowing. Thus, the oral cavity is a reservoir of EBV flow.

The dynamics of IFN-α and -γ production were studied before the Ingaron therapy and 1 and 3 months after the end of the course. The levels of IFN-α and -γ in blood serum were determined, as well as spontaneous and induced production of these cytokines in a culture of blood lymphocytes. Newcastle disease virus (obtained at the L.A. Tarasevich State Research Institute for Standardization and Control of Medical Biological Preparations, St. Petersburg) with an infectious titer of 8 lg EID/0.2 ml in a volume of 8 μl per well was used as an inducer of IFN-α production. Phytohemagglutinin (PHA-P) from PanEco (Russia) at a dose of 10 μg/ml was used as an inducer of IFN-γ production. The quantitative content of cytokines was determined in the serum and supernatant of a 24-hour whole blood culture by enzyme-linked immunosorbent assay using the test systems alpha-Interferon-ELISA-BEST and gamma-Interferon-ELISA-BEST manufactured by Vector Best (Russia). The test system

DOI: https://doi.org/10.17816/brmma71302

manufacturer provides reference values for spontaneous, serum, and induced IFN-α and IFN-γ production.

Statistical analysis of the results obtained was performed using the software package IBM SPSS Statistics, version 26. Group results are presented as mean ± standard error of the mean (*M* ± Standard Error). Parametric (Pearson's method) and nonparametric (tau (τ) Kendall) criteria were used. The critical significance level of the difference in indicators was equal to 0.05.

RESULTS AND DISCUSSION

EBV infection was confirmed in all patients by PCR reaction in saliva samples. The average concentration of EBV DNA was 177369.51 ± 65615.21 copies/ml. Ingaron was administered at a dose of 500,000 IU intramuscularly once a day every other day for 20 days (10 injections total). Before Ingaron therapy, 1 and 3 months after the end of therapy, the content of INF-α and -γ (spontaneous, serum, and induced) in the culture of lymphocytes was determined (Tables 1 and 2), and the data obtained are presented.

One month after the end of Ingaron therapy, there is a tendency toward an increase in spontaneous production of IFN-α (statistically insignificant); after 3 months, the values return to the initial figures. The level of serum production of IFN-α did not change after 1 and 3 months, remaining within the normal range. There was a tendency to increase the induced production of IFN-α 1 month after the end of therapy, followed by the level normalization after 3 months. Thus, Ingaron does not significantly affect the production of IFN-α in the general group of patients after 1 and 3 months of therapy.

It was revealed that in the general group of patients after Ingaron therapy, after 1 month, the serum ($p = 0.024$) IFN-γ production increased. After 3 months, the serum level almost returned to its baseline value. The level of spontaneous production 1 and 3 months after the end of therapy did not change significantly. Induced IFN-γ production also tended to increase 1 and 3 months after the end of therapy without significant changes ($p = 0.38$ and $p = 0.27$, respectively).

Table 1. Dynamics of IFN-α production before the onset, one and three months after ingaron therapy in the general group of chronic Epstein – Barr virus infection patients, pg/ml
Таблица 1. Динамика продукции интерферона-альфа (IFN-α) до начала, через 1 и 3 месяца после терапии ингароном в общей группе больных хронической инфекцией вируса Эпштейна – Барр, пг/мл

Parameter	Before therapy	1 month after therapy	3 months after therapy	*p*
Spontaneous IFN-α	3.76 ± 0.58	5.80 ± 4.02	3.85 ± 19.24	1. 2 = 0.345 2. 3 = 0.435 1. 3 = 0.359
Serum IFN-α	5.09 ± 1.47	4.21 ± 0.7	5.57 ± 1.2	1. 2 = 0.289 2. 3 = 0.202 1. 3 = 0.38
Induced IFN-α	296.78 ± 127.43	578.154 ± 129.46	294.78 ± 60.67	1. 2 = 0.284 2. 3 = 0.360 1. 3 = 0.145

Table 2. Dynamics of IFN-γ production before the onset, one and three months after ingaron therapy in the general group of chronic Epstein – Barr virus infection patients, pg/ml
Таблица 2. Динамика продукцииинтерферона-γ (IFN-γ) до начала, через один и три месяца после терапии ингароном в общей группе больных хронической инфекцией вируса Эпштейна – Барр, пг/мл

Parameter	Before therapy	1 month after therapy	3 months after therapy	*p*
Spontaneous IFN-γ	2.07 ± 0.26	2.57 ± 0. 75	2.00 ± .57	1. 2 = 0.34 1. 3 = 0.36 2. 3 = 0.57
Serum IFN-γ	1.85 ± 0.14	5.57 ± 1.20	2.10 ± 0.68	1. 2 = 0.024 1. 3 = 0.21 2. 3 = 0.38
Induced IFN-γ	1862.72 ± 624.52	2487.96 ± 437.73	4308.12 ± 3053.77	1. 2 = 0.38 1. 3 = 0.38 2. 3 = 0.27

DOI: https://doi.org/10.17816/brmma71302

However, the analysis of the initial data on the levels of induced IFN-γ showed that these values differed sharply in all patients, i.e., they were at the level of the lower limit of the reference values or closer to the upper limit of the values (281–4335 pg/ml). In this regard, the general group of patients was distributed into two groups by the induced production of IFN-γ before the start of therapy (group 1 (n = 30) with the level of induced IFN-γ of 2706 ± 1058.94 pg/ml and group 2 (n = 21) with that of 287.2 ± 64.65 pg/ml).

It was established that after a course of therapy with Ingaron in group 1, the level of induced IFN-γ tended to decrease gradually. In contrast, in group 2, there was a significant increase in the level of induced IFN-γ 3 months after therapy (p = 0.027). At the same time, the IFN-γ levels in both groups remained within the reference values (Fig. 1).

The values of the spontaneous level of IFN-γ in both groups increased significantly after 1 month, remaining at these values in group 1 and tending to decrease after 3 months in group 2. However, these values in both groups did not differ from the reference values (0–6 pg/ml, Fig. 2).

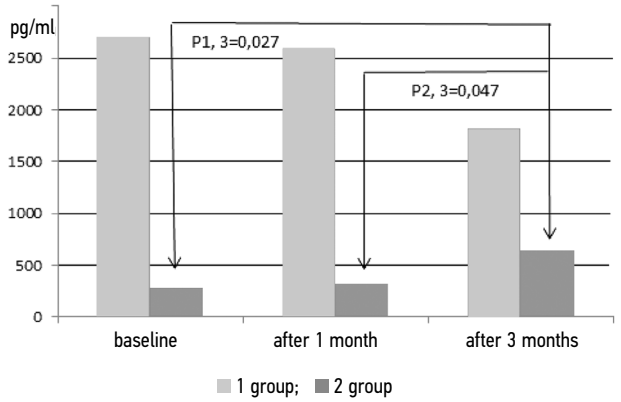

Fig. 1. Dynamics of the level of induced IFN-γ before, one and three months after ingaron therapy in patients of the 1st and 2nd groups of chronic Epstein – Barr virus infection

Рис. 1. Динамика уровня индуцированного IFN-γ до начала, через один и три месяца после терапии ингароном у больных хронической инфекцией вируса Эпштейна – Барр 1-й и 2-й групп

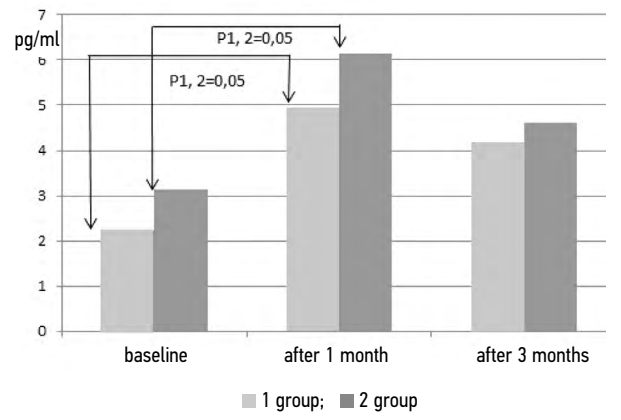

Fig. 2. Dynamics of the level of spontaneous IFN-γ before, one and three months after ingaron therapy in patients in groups 1 and 2 of chronic Epstein – Barr virus infection

Рис. 2. Динамика уровня спонтанного IFN-γ до начала, через один и три месяца после терапии ингароном у больных хронической инфекцией вируса Эпштейна – Барр в 1-й и 2-й группах

It was revealed that in both groups, the increase in serum IFN-γ production was significant 1 month after the end of therapy (p = 0.03 and p = 0.02, respectively). In contrast, after 3 months, there was a tendency to an insignificant decrease in serum IFN-γ, while the data obtained did not differ from the initial data before the start of therapy and from the reference values provided by the test system manufacturer (0–10 pg/ml, Fig. 3).

It was established that in patients of group 1, after 1 and 3 months of therapy with Ingaron, there was a significant decrease in subfebrile temperature, sore throat, algor, hyperhidrosis, and a decrease in mental alertness. The remaining complaints tended to decrease or remained unchanged (Table 3).

In group 2 patients, 1 and 3 months after Ingaron therapy, there was significant improvement of the leading clinical complaints, in particular, a decrease in lymphadenitis, sore throat, algor, hyperhidrosis, mucus drip along the posterior pharynx, stomatitis, joint pain, decreased alertness, and sleep disturbances (Table 4).

Consequently, group 2 patients with a reduced level of induced IFN-γ before Ingaron therapy had a more pronounced response to therapy. Group 1 patients with initially high induced IFN-γ production had more pronounced clinical manifestations.

Correlation analysis of the effect of the baseline level of induced IFN-γ on the clinical presentation of the disease in patients of both groups revealed that a high level of induced IFN-γ in group 1 affects the development of hyperhidrosis inversely in patients (r = –0.506, p = 0.023; τ = –0.419, p = 0.021). In group 2, the initially low level of induced IFN-γ affects the development of asthenia (r = –0.405, p = 0.045; τ = –0.419, p = 0.037) inversely. No other significant correlations were identified.

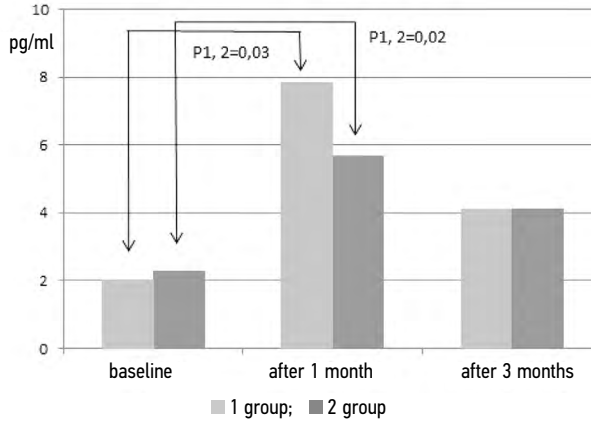

Fig. 3. Dynamics of serum IFN-γ level before, one and three months after ingaron therapy in patients in groups 1 and 2 of chronic Epstein – Barr virus infection

Рис. 3. Динамика уровня сывороточного IFN-γ до начала, через один и три месяца после терапии ингароном у больных хронической инфекцией вируса Эпштейна – Барр в 1-й и 2-й группах

DOI: https://doi.org/10.17816/brmma71302

Таблица 3. Частота основных клинических жалоб у 1-й группы больных хронической инфекцией вируса Эпштейна – Барр до начала терапии ингароном и через 1 и 3 месяца после ее окончания, % (*n* = 30)

Table 3. The frequency of the main clinical complaints in patients of the 1st group of chronic Epstein – Barr virus infection before the start of therapy with ingaron and one and three months after its completion, % (*n* = 30)

Frequency of complaints	Before therapy (*n* = 21)	1 month after therapy	3 months after therapy	*p*
Subfebrile temperature	83.33	30.76	30.76	1. 2 = 0.004 1. 3 = 0.004 2. 3 = 0.000
Lymphadenitis	53.33	43.33	26.66	1. 2 = 0.082 1. 3 = 0.047 2. 3 = 0.05
Sore throat	93.33	43.33	36.66	1. 2 = 0.001 1. 3 = 0.001 2. 3 = 0.058
Asthenia	76.66	66.66	53.33	1. 2 = 0.054 1. 3 = 0.001 2. 3 = 0.064
Algor	70.00	13.33	20.00	1. 2 = 0.001 1. 3 = 0.001 2. 3 = 0.064
Hyperhidrosis	93.33	53.33	46.66	1. 2 = 0.001 1. 3 = 0.001 2. 3 = 0.056
Mucus dripping	33.33	13.33	16.66	1. 2 = 0.05 1. 3 = 0.054 2. 3 = 0.74
Stomatitis	36.66	16.66	20.00	1. 2 = 0.052 1. 3 = 0.068 2. 3 = 0.07
Joint pain	26.66	20.00	23.33	1. 2 = 0.058 1. 3 = 0.104 2. 3 = 0.074
Irritability and tearfulness	70.00	56.66	53.33	1. 2 = 0.058 1. 3 = 0.052 2. 3 = 0.076
Eruption on the skin	56.66	53.33	46.66	1. 2 = 0.058 1. 3 = 0.052 2. 3 = 0.072
Headaches, dizziness	36.66	20.00	16.66	1. 2 = 0.068 1. 3 = 0.052 2. 3 = 0.07
Decreased alertness, defective memory	56.66	40.00	36.66	1. 2 = 0.052 1. 3 = 0.05 2. 3 = 0.056
Sleep disorder	46.66	40.00	36.66	1. 2 = 0.058 1. 3 = 0.07 2. 3 = 0.072

Primary viral infections induce antiviral immune responses from the host; however, these responses may not be sufficient to eliminate the virus since the virus persistence leads to suppression of antiviral immune responses. One of the mechanisms for suppressing the antiviral response is cytotoxic lymphocytes, including NK cells and $CD8^+$ T cells, which express membrane molecules. At the same time, expression is induced in infected or transformed cells. The sensor for such kill-me signals is the natural killer group type 2 lectin-like transmembrane receptor, member D (NKG2D), expressed on NK, $CD8^+$ T cells, and γδ T cells. The expression of the NKG2D ligand is regulated at the transcriptional, posttranscriptional, and posttranslational levels [26, 27]. Interaction of NKG2D with NK cells induces degranulation, cytotoxic reaction, and production of cytokines by NK cells and some T cells [26]. In the case of viral infection, the expression of NKG2D ligands (NKG2D-Ls) decreases, which is mediated by viruses, which

allows the virus to avoid the antiviral immune response from the host [28]. It has been revealed that the early EBV protein BZLF1 can block IFN-γ production by inhibiting the downstream IFN-γ signaling pathway. BZLF1 abolishes the transcription of all expressed HLA class II molecules, inhibits IFN-γ-induced STAT1 tyrosine phosphorylation and BZLF1 nuclear translocation, and reduces IFN-γ receptor expression, stimulating a mechanism by which EBV can avoid an antiviral immune response during primary infection [29]. Cytokine signaling is a very early response to viral infection and may explain the presence of appropriate inhibitory viral factors in the tegument.

Thus, the dysregulation of proinflammatory cytokine production is based on the fact that virions already contain molecules that directly target proper cytokine signaling [30]. INF-γ, having direct antiviral activity, is an effective therapeutic agent in treating viral infection [31]. After therapy with recombinant IFN-γ in a patient with infectious mononucleosis and X-linked lymphoproliferative syndrome, there was a positive trend in the reduction of

Table 4. The frequency of clinical complaints in patients of the 2nd group of chronic Epstein – Barr virus infection before the start of therapy with ingaron and one and three months after its completion, % (*n* = 21)
Таблица 4. Частота клинических жалоб у 2-й группы больных хронической инфекцией вируса Эпштейна – Барр до начала терапии ингароном и через 1 и 3 месяца после ее окончания, % (*n* = 21)

Frequency of complaints	Before therapy (*n* = 21)	1 month after the end of therapy	3 months after the end of therapy	*p*
Subfebrile temperature	57.14	33.33	28.57	1. 2 = 0.073 1. 3 = 0.058 2. 3 = 0.072
Lymphadenitis	66.66	14.28	19.04	1. 2 = 0.002 1. 3 = 0.05 2. 3 = 0.078
Sore throat	33.33	23.80	19.04	1. 3 = 0.002 1. 3 = 0.002 2. 3 = 0.064
Asthenia	61.90	52.38	57.14	1. 2 = 0.073 1. 3 = 0.078 2. 3 = 0.102
Algor	47.67	28.57	23.80	1. 2 = 0.001 1. 3 = 0.001 2. 3 = 0.104
Hyperhidrosis	61.90	52.38	47.67	1. 2 = 0.029 1. 3 = 0.001 2. 3 = 0.072
Mucus dripping	21.05	10.52	10.52	1. 2 = 0.029 1. 3 = 0.029 2. 3 = 0.104
Stomatitis	15.78	10.52	9.52	1.2 = 0.004 1.3 = 0.001 2.3 = 0.106
Joint pain	15.78	10.52	9.52	1. 2 = 0.004 1. 3 = 0.001 2. 3 = 0.106
Irritability and tearfulness	42.11	21.05	26.31	1. 2 = 0.054 1. 3 = 0.058 2. 3 = 0.074
Eruption on the skin	42.11	26.31	23.80	1. 2 = 0.056 1. 3 = 0.054 2. 3 = 0.108
Headaches, dizziness	26.31	23.80	21.05	1. 2 = 0.074 1. 3 = 0.074 2. 3 = 0.078
Decreased alertness, defective memory	33.33	23.80	26.31	1. 2 = 0.002 1. 3 = 0.068 2. 3 = 0.072
Sleep disorder	15.78	14.28	10.52	1. 2 = 0.078 1. 3 = 0.004 2. 3 = 0.046

DOI: https://doi.org/10.17816/brmma71302

virus-infected cells and a linear increase in the level of IFN-γ in blood serum. NK cell activity remained within the normal range throughout therapy. The authors suggested that cytotoxic cells can produce endogenous IFN-γ [32]. A. Linde et al. [33] revealed an increase in the serum level of IFN-γ 24 and 48 hours after EBV infection. Then, the level of IFN-γ returned to its baseline values. M. Hornef et al. [34] demonstrated that in patients with acute infectious mononucleosis, an increase in the level of serum IFN-γ was registered only during week 1 from the moment of infection, after which the IFN-γ level returned to normal. Exciting data were obtained when studying the dynamics of IFN-γ production in patients with tuberculosis, who had a decrease in the average level of IFN-γ over time. However, this decrease occurred during the first 8 weeks of a specific therapy. When the initially susceptible 55 patients were compared with the drug-resistant 18 patients, no difference was noted in the IFN-γ levels over time. Since the production of IFN-γ and secretion from T cells increases in response to an increase in antigenic load and then stabilizes over 24 weeks, a decrease in the concentration of IFN-γ may indicate a positive response to ongoing therapy and function as monitoring of response to therapy [35].

Analysis of our results separately in each group of patients showed that in the group with an initially low level, the administration of Ingaron led to a significant increase in the level of induced INF-γ 3 months after the end of therapy. This increase is probably due to a more pronounced response to Ingaron therapy, manifested by a significant improvement in the primary clinical complaints. Thus, the dynamics of production of the initially low level of induced INF-γ may be a marker of the positive effect of the ongoing therapy with Ingaron. The absence of improvement in the increase in the production of induced INF-γ in the general group of patients 1 and 3 months after the end of Ingaron therapy indicates the absence of an effect of the drug on the level of endogenous INF-γ, which was previously demonstrated in studies by other authors. At the same time, Ingaron has a pronounced antiviral effect, which was revealed earlier, and does not cause an increase in INF-γ production to levels that would exceed the reference values.

CONCLUSION

1. Antiviral therapy with Ingaron 1 and 3 months after the end of treatment of CEBVI patients does not cause changes in the production of IFN-α and -γ to levels that would exceed the reference values in this category of patients.
2. In group 2 CEBVI patients, Ingaron therapy leads to a significant increase in the level of induced IFN-γ 3 months after the end of antiviral therapy.
3. The positive dynamics of production of the initially low level of induced IFN-γ may be a marker of the efficiency of Ingaron therapy in CEBVI patients.
4. All patients after therapy with Ingaron showed a significant decrease in clinical complaints. The most pronounced improvement was revealed in patients with initially low levels of induced IFN-γ.
5. Ingaron can treat CEBVI patients at a dose of 500,000 IU every other day with at least 10 injections.

REFERENCES

1. Biron C, Sen G. *Interferons and other cytokines. Fields virology*. 4th ed. Philadelphia, Pa: Lippincott-Raven; 2001.

2. Sen GC. Viruses and Interferons. *Ann Rev Microbiol*. 2001;(55):255–281. DOI: 10.1146/annurev.micro.55.1.255

3. Hill N, Sarvetnick N. Cytokines: promoters and dampeners of autoimmunity. *Curr Open Immunol.* 2002; 14(6):791–797. DOI: 10.1016/s0952-7915(02)00403-x

4. Gattoni A, Parlato A, Vangieri B, et al. Interferon-gamma: biologic functions and HCV therapy (type I/II) (1 of 2 parts). *Clin Ter.* 2006;157(4):377–386.

5. Schoenborn J, Wilson C. Regulation of interferon-gamma during innate and adaptive immune responses. *Adv Immunol.* 2007;(96):41–101. DOI: 10.1016/S0065-2776(07)96002-2

6. Roff S, Noon-Song E, Yamamoto J. The significance of interferon-gamma in HIV-1 pathogenesis, therapy, and prophylaxis. *Front Immunol.* 2014;(4):498. DOI: 10.3389/fimmu.2013.00498

7. Fan-ching L, Howard A. Young, Interferons Success in anti-viral immunotherapy. *Cytokine Growth Factor Rev.* 2014;25(4):369–376. DOI: 10.1016/j.cytogfr.2014.07.015

8. Soowon K, Hailey M, Seungmin H. Direct antiviral mechanisms of Interferon-Gamma. *Immune Netw.* 2018;18(5):e33. DOI: 10.4110/in.2018.18.e33.

9. Fujisaki T, Nagafuchi S, Okamura T. Gamma-interferon for severe chronic active Epstein – Barr virus. *Ann Intern Med.* 1993;118(6):474–475. DOI: 10.7326/0003-4819-118-6-199303150-00022

10. Andersson J. Clinical and immunological considerations in Epstein – Barr virus-associated diseases. *Scand J Infect Dis Suppl.* 1996;(100):72–82.

11. Balachandra K, Thawaranantha D, Ayuthaya P, et al. Effects of human alpha, beta and gamma interferons on varicella zoster virus in vitro. *South As J Trop Med Publ Health.* 1994;25(2):252–257.

12. Schroder K, Hertzog P, Ravasi T, et al. Interferon-gamma: an overview of signals, mechanisms and functions. *J Leukoc Biol.* 2004;75(2):163–189. DOI: 10.1189/jlb.0603252

13. Maleev VV, Shmelev VA, Gindis AA, et al. Modern approaches to the therapy of shingles. Interferon-gamma in the treatment of genital herpes. *Infekcionnye bolezni.* 2007;5(3):28–32. (In Russ.).

14. Rakityanskaya IA, Ryabova TS, Todzhibaev UA, et al. The effect of Ingaron on the dynamics of the number of copies of deoxyribonucleic acid Epstein–Barr virus in saliva samples and on the manifestation of clinical symptoms in patients with chronic Epstein – Barr virus infection. *Vestnik Rossijskoj Voenno-Medicinskoj Akademii.* 2019;2(65):18–23. (In Russ.).

15. Lotz M, Tsoukas C, Fong S, et al. Regulation of Epstein-Barr virus infection by recombinant interferons. Selected sensitivity to interferon-gamma. *Eur J Immunol.* 1985;15(5):520–525. DOI: 10.1002/eji.1830150518

16. Sainz B, Halford W. Alpha/Beta interferon and gamma interferon synergize to inhibit the replication of herpes simplex virus type 1. *J Virol.* 2002;76 (22):11541–11550. DOI: 10.1128/jvi.76.22.11541-11550.2002

17. Patterson C, Lawrence D, Echols L, et al. Immune-mediated protection from measles virus-induced central nervous system disease is noncytolytic and gamma interferon dependent. *J Virol.* 2002;(76):4497–4506. DOI: 10.1128/JVI.76.9.4497-4506.2002

18. Rakityanskaya IA, Ryabova TS, Kalashnikova AA. Influence of ingaron on the dynamics of interferon-α and -γ production and on the manifestation of clinical symptoms in patients with chronic virus Epsthtein – Barr infection. *Voprosi Virusologi.* 2019;64(1):23–29. (In Russ.).

19. Holmes G, Kaplan J, Gantz N, et al. Chronic fatigue syndrome: a working case definition. *Ann Intern Med.* 1988;108(3):387–389. DOI: 10.7326/0003-4819-108-3-387

20. Fukuda K, Straus S, Hickie I, et al. The chronic fatigue syndrome: a comprehensive approach to its definition and study. International Chronic Fatigue Syndrome Study Group. *Ann Intern Med.* 1994;121(12):953–959. DOI: 10.7326/0003-4819-121-12-199412150-00009

21. Staines D. Postulated vasoactive neuropeptide autoimmunity in fatigue-related conditions: A brief review and hypothesis. *Clin Dev Immunol.* 2006;13(1):25–39. DOI: 10.1080/17402520600568252

22. Griffith J, Zarrouf A. A systematic review of chronic fatigue syndrome: don't assume it's depression. *J Clin Psychiatry.* 2008;(1):120–128. DOI: 10.4088/pcc.v10n0206

23. Kimura H. Pathogenesis of chronic active Epstein – Barr virus infection: is this an infectious disease, lymphoproliferative disorder, or immunodeficiency? *Rev Med Virol.* 2006;(16):251–261. DOI: 10.1002/rmv.505

24. Kimura H, Cohen J. Chronic active Epstein – Barr virus disease. *Front Immunol.* 2017;(28):1–6. DOI: 10.3389/fimmu.2017.01867

25. Laichalk L, Hochberg D, Babcock G, et al. The dispersal of mucosal memory B cells: evidence from persistent EBV infection. *Immunity* 2002;16 (5):745–754. DOI: 10.1016/S1074-7613(02)00318-7

26. Raulet D, Gasser S, Gowen B, et al. Regulation of ligands for the NKG2D activating receptor. *An Rev Immunol.* 2013;(31):413–441. DOI: 10.1146/annurev-immunol-032712-095951

27. Simon O, Seliger B. Molecular mechanisms of human herpes viruses inferring with host immune surveillance. *J Immunother Cancer.* 2020;8(2):e000841. DOI: 10.1136/jitc-2020-000841

28. Ghadially H, Brown L, Lloyd C, et al. MHC class I chain-related protein A and B (MICA and MICB) are predominantly expressed intracellularly in tumour and normal tissue. *Br J Cancer.* 2017;116:1208–1217. DOI: 10.1038/bjc.2017.79

29. Barbu M, Condrat C, Thompson D, et al. Microrna involvement in signaling pathways during viral infection. *Front Cell Dev Biol.* 2020;8:143. DOI: 10.3389/fcell.2020.00143

30. Skinner C, Ivanov N, Barr S, et al. An Epstein – Barr virus microRNA blocks interleukin-1 (IL-1) signaling by targeting IL-1 receptor 1. *J Virol.* 2017;(91):e00530–17. DOI: 10.1128/JVI.00530-17

31. Abboud G. Tahiliani V, Desai P, et al. Natural killer cells and innate interferon gamma participate in the host defense against respiratory vaccinia virus infection. *J Virol.* 2016;90(1):129–141. DOI: 10.1128/JVI.01894-15

32. Okano M, Thiele G, Kobayashi R, et al. Interferon-gamma in a family with X-linked lymphoproliferative syndrome with acute Epstein – Barr virus infection. *J Clin Immunol.* 1989;9(1):48–54. DOI: 10.1007/BF00917127

33. Linde A, Andersson B, Svenson S, et al. Serum levels of lymphokines and soluble cellular receptors in primary Epstein – Barr virus infection and in patients with chronic fatigue syndrome. *J Infect Dis.* 1992;165(6):994–1000. DOI: 10.1093/infdis/165.6.994

34. Hornef MW, Wagner HJ, Kruse A, et al. Cytokine production in a whole-blood assay after Epstein – Barr virus infection in vivo. *Clin Diagn Lab Immunol.* 1995;2(2):209–213.

35. Liang L, Shi R, Xin L, et al. Interferon-Gamma response to treatment of active pulmonary and extrapulmonary tuberculosis. *J Tuberc Lung Dis.* 2017;21(10):1145–1149. DOI: 10.5588/ijtld.16.0880

СПИСОК ЛИТЕРАТУРЫ

1. Biron C., Sen G.C. Interferons and other cytokines. Fields virology. 4th ed. Philadelphia, Pa: Lippincott-Raven, 2001.

2. Sen G.C. Viruses and Interferons // Ann. Rev. Microbiol. 2001. Vol. 55. P. 255–281. DOI: 10.1146/annurev.micro.55.1.255

3. Hill N., Sarvetnick N. Cytokines: promoters and dampeners of autoimmunity // Curr. Open Immunol. 2002. Vol. 14. No. 6. P. 791–797. DOI: 10.1016/s0952-7915(02)00403-x

4. Gattoni A., Parlato A., Vangieri B., et al. Interferon-gamma: biologic functions and HCV therapy (type I/II) (1 of 2 parts) // Clin. Ter. 2006. Vol. 157. No. 4. P. 377–386.

5. Schoenborn J., Wilson C. Regulation of interferon-gamma during innate and adaptive immune responses // Adv. Immunol. 2007. No. 96. P. 41–101. DOI: 10.1016/S0065-2776(07)96002-2

6. Roff S, Noon-Song E, Yamamoto J. The significance of interferon-gamma in HIV-1 pathogenesis, therapy, and prophylaxis // Front. Immunol. 2014. No. 4. P. 498. DOI: 10.3389/fimmu.2013.00498

7. Fan-Ching L., Howard A. Young, Interferons Success in anti-viral immunotherapy // Cytokine Growth Factor Rev. 2014. Vol. 25. No. 4. P. 369–376. DOI: 10.1016/j.cytogfr.2014.07.015

8. Soowon K., Hailey M., Seungmin H. Direct antiviral mechanisms of Interferon-Gamma // Immune Netw. 2018. Vol. 18. No. 5. P. e33. DOI: 10.4110/in.2018.18.e33

9. Fujisaki T., Nagafuchi S., Okamura T. Gamma-interferon for severe chronic active Epstein – Barr virus // Ann. Intern. Med. 1993. Vol. 118. No. 6. P. 474–475. DOI: 10.7326/0003-4819-118-6-199303150-00022

10. Andersson J. Clinical and immunological considerations in Epstein-Barr virus-associated diseases // Scand. J. Infect. Dis. Suppl. 1996. No. 100. P. 72–82.

11. Balachandra K., Thawaranantha D., Ayuthaya P., et al. Effects of human alpha, beta and gamma interferons on varicella zoster virus in vitro // South As. J. Trop. Med. Publ. Health. 1994. Vol. 25. No. 2. P. 252–257.

12. Schroder K., Hertzog P., Ravasi T., et al. Interferon-gamma: an overview of signals, mechanisms and functions // J. Leukoc. Biol. 2004. Vol. 75. No. 2. P. 163–189. DOI: 10.1189/jlb.0603252

13. Малеев В.В., Шмелев В.А., Гиндис А.А., и др. Современные подходы к терапии опоясывающего лишая. Интерферон-гамма в терапии генитального герпеса // Инф. болезни. 2007. Т. 5, № 2. С. 28–32.

14. Ракитянская И.А., Рябова Т.С., Тоджибаев У.А., и др. Влияние ингарона на динамику копий дезоксирибонуклеиновой кислоты вируса Эпштейна – Барр в образцах слюны и клинические проявления // Вестник Российской военно-медицинской академии. 2019. Т. 66, № 2. С. 18–23.

15. Lotz M., Tsoukas C., Fong S., et al. Regulation of Epstein-Barr virus infection by recombinant interferons. Selected sensitivity to interferon-gamma // Eur. J. Immunol. 1985. Vol. 15. No. 5. P. 520–525. DOI: 10.1002/eji.1830150518

16. Sainz B., Halford W. Alpha/Beta interferon and gamma interferon synergize to inhibit the replication of herpes simplex virus type 1 // J. Virol. 2002. Vol. 76. No. 22. P. 11541–11550. DOI: 10.1128/jvi.76.22.11541-11550.2002

17. Patterson C., Lawrence D., Echols L., et al. Immune-mediated protection from measles virus-induced central nervous system disease is noncytolytic and gamma interferon dependent // J. Virol. 2002. Vol. 76. P. 4497–4506. DOI: 10.1128/JVI.76.9.4497-4506.2002

18. Ракитянская И.А., Рябова Т.С., Калашникова А.А. Влияние ингарона на продукцию интерферона-альфа и -гамма и на проявление клинических симптомов у больных хронической вирусной Эпштейна – Барр инфекцией. Вопросы вирусологии. 2019. Т. 64, № 1. С. 16–23.

19. Holmes G., Kaplan J., Gantz N., et al. Chronic fatigue syndrome: a working case definition // Ann. Intern. Med. 1988. Vol. 108. No. 3. P. 387–389. DOI: 10.7326/0003-4819-108-3-387

20. Fukuda K., Straus S., Hickie I., et al. The chronic fatigue syndrome: a comprehensive approach to its definition and study. International Chronic Fatigue Syndrome Study Group // Ann. Intern. Med. 1994. Vol. 121. No. 12. P. 953–959. DOI: 10.7326/0003-4819-121-12-199412150-00009

21. Staines D. Postulated vasoactive neuropeptide autoimmunity in fatigue-related conditions: A brief review and hypothesis // Clin. Dev. Immunol. 2006. Vol. 13. No. 1. P. 25–39. DOI: 10.1080/17402520600568252

22. Griffith J., Zarrouf A. A systematic review of chronic fatigue syndrome: don't assume it's depression // J. Clin. Psychiatry. 2008. Vol. 1. P. 120–128. DOI: 10.4088/pcc.v10n0206

23. Kimura H. Pathogenesis of chronic active Epstein – Barr virus infection: is this an infectious disease, lymphoproliferative disorder, or immunodeficiency? // Rev. Med. Virol. 2006. Vol. 16. P. 251–261. DOI: 10.1002/rmv.505

24. Kimura H., Cohen J. Chronic active Epstein – Barr virus disease // Front. Immunol. 2017. Vol. 28. P. 1–6. DOI: 10.3389/fimmu.2017.01867

25. Laichalk L., Hochberg D., Babcock G., et al. The dispersal of mucosal memory B cells: evidence from persistent EBV infection // Immunity. 2002. Vol. 16. No. 5. P. 745–754. DOI: 10.1016/S1074-7613(02)00318-7

26. Raulet D., Gasser S., Gowen B., et al. Regulation of ligands for the NKG2D activating receptor // An. Rev. Immunol. 2013. Vol. 31. P. 413–441. DOI: 10.1146/annurev-immunol-032712-095951

27. Simon O., Seliger B. Molecular mechanisms of human herpes viruses inferring with host immune surveillance // J. Immunother. Cancer. 2020. Vol. 8. No. 2. P. e000841. DOI: 10.1136/jitc-2020-000841

28. Ghadially H., Brown L., Lloyd C., et al. MHC class I chain-related protein A and B (MICA and MICB) are predominantly expressed intracellularly in tumour and normal tissue // Br. J. Cancer. 2017. Vol. 116. P. 1208–1217. DOI: 10.1038/bjc.2017.79

29. Barbu M., Condrat C., Thompson D., et al. Microrna involvement in signaling pathways during viral infection // Front. Cell. Dev. Biol. 2020. Vol. 8. P. 143. DOI: 10.3389/fcell.2020.00143

30. Skinner C., Ivanov N., Barr S., et al. An Epstein – Barr virus microRNA blocks interleukin-1 (IL-1) signaling by targeting IL-1 receptor 1 // J. Virol. 2017. Vol. 91. P. e00530–17. DOI: 10.1128/JVI.00530-17

31. Abboud G., Tahiliani V., Desai P., et al. Natural killer cells and innate interferon gamma participate in the host defense against respiratory vaccinia virus infection // J. Virol. 2016. Vol. 90. No. 1. P. 129–141. DOI: 10.1128/JVI.01894-15

32. Okano M., Thiele G., Kobayashi R., et al. Interferon-gamma in a family with X-linked lymphoproliferative syndrome with acute Epstein – Barr virus infection // J. Clin. Immunol. 1989. Vol. 9. No. 1. P. 48–54. DOI: 10.1007/BF00917127

33. Linde A., Andersson B., Svenson S., et al. Serum levels of lymphokines and soluble cellular receptors in primary Epstein – Barr virus

infection and in patients with chronic fatigue syndrome // J. Infect. Dis. 1992. Vol. 165. No. 6. P. 994–1000. DOI: 10.1093/infdis/165.6.994

34. Hornef M.W., Wagner H.J., Kruse A., et al. Cytokine production in a whole-blood assay after Epstein – Barr virus infection in vivo // Clin. Diagn. Lab. Immunol. 1995. Vol. 2. No. 2. P. 209–213.

35. Liang L., Shi R., Xin L., et al. Interferon-Gamma response to treatment of active pulmonary and extrapulmonary tuberculosis // J. Tuberc. Lung. Dis. 2017. Vol. 21. No. 10. P. 1145–1149. DOI: 10.5588/ijtld.16.0880

ОБ АВТОРАХ

***Андрей Сергеевич Мануилов,** старший ординатор; e-mail: andre.manuilov@yandex.ru

Ирина Анисимовна Ракитянская, доктор медицинских наук; e-mail: tat-akyla@inbox.ru

Татьяна Сергеевна Рябова, доктор медицинских наук, доцент; e-mail: tita74@ mail.ru

Анастасия Андреевна Калашникова, кандидат биологических наук; e-mail: petkova_nas@mail.ru

Андрей Николаевич Бельских, доктор медицинских наук, профессор; e-mail: belsky@gmail.com

Апчел Андрей Васильевич, доктор медицинских наук

AUTHORS INFO

***Andrey S. Manuilov,** senior resident; e-mail: andre.manuilov@yandex.ru

Irina A. Rakityanskaya, doctor of medical sciences; e-mail: tat-akyla@inbox.ru

Tatyana S. Ryabova, doctor of medical sciences, associate professor; e-mail: tita74 @ mail.ru

Anastasia A. Kalashnikova, candidate of biological sciences; e-mail: petkova_nas@mail.ru

Andrey N. Bel'skikh, doctor of medical sciences, professor; e-mail: belsky@gmail.com

Andrey V. Apchel, doctor of medical sciences

* Corresponding author / Автор, ответственный за переписку