O.I. SKROTSKA, I.V. Lych, V.M. Solominchuk, N.M. Zholobak*

National University of Food Technologies

**Institute of Microbiology and Virology by D.K. Zabolotny of NAS of Ukraine*

IMMUNOTHERAPEUTIC APPROACHES IN THE TREATMENT OF HERPETIC INFECTIONS

Today herpetic infections take place among the most common viral diseases that significantly suppress the immune system. About 90% of the world's population are infected with one or more serovariants of viruses of herpes type. In body of people with healthy immune systems herpesviruses (HV) can circulate without symptoms, but for people of immunosuppressive conditions they cause severe fatal diseases. Infection with HV can lead to serious diseases such as hepatitis, meningitis and encephalitis. Most of these effects are led to after infection with HV of newborns, including central nervous system affection with 50% of mortality, and generalized HV infection that leads to 60% of fatal outcomes within the first year of life. According to World Health Organization, herpes infections mortality among viral diseases ranks second to hepatitis [1].

HV is polytropic agents, particularly herpes simplex virus of I and II types (HSV-1, HSV-2). This virus infects the central nervous system, skin, mucous membranes, genital organs, liver and others. Particularly severe are the affections of central nervous system with HV – meningitis and encephalitis, characterized by a large percentage of mortality and disability. Pathology of HV infection is caused mainly by direct cytopathic effect of the virus, which results in cell lysis and focal necrosis of the infected area. In tissues capable of regeneration, cytopathic effect of HV is exteremely dangerous if the virus damage does not completely destroy the organ or leads to functional failure of infected organs during illness. However, the brain's ability to regenerate damaged tissues is low, and extensive necrosis induced by HV, leads to fatal consequences. There is a delicate balance between direct HV-

induced pathology and immunopathology, caused by immune responses to the virus. Feeble immune response to virus infection leads to severe HV infection through massive replication of the virus and its contagion. Enhanced immune response can lead to greater symptoms of infection, high intracerebral pressure or pulmonary complications [2].

Extreme extendability and politropic form of HV, its lifelong persistence in the body and frequent relapses of diseases, caused by it, indicate the need for a highly efficient and safe means of preventing and treating these diseases. Pathogenic implementation of modern immunotherapy is fundamental ability to manage the formation and the level of intensity of the immune response to herpesvirus antigens. Today in Ukraine there are commonly used such drugs as immunoglobulins, interferons (IFN), IFN inducers and immunomodulators for immunotherapy of herpesvirus infections.

The mechanism of action of immunoglobulins is to neutralize herpes virions, enhancing phagocytosis HV, as well as in promoting the destruction of virus-infected cells in antibody-mediated cytotoxicity reactions. Immunoglobulin preparations are also characterized by desensitization, immunomodulatory and detoxifying action.

IFN are cytokines that have antiviral, immunomodulatory and antitumor activity. They affect a number of processes, including the regulation of cell growth, differentiation, apoptosis, are indirectly involved in the development of the immune response, and enable mechanisms of antibacterial protection. These properties of IFN allow to assign them to polyfunctional bioregulators of broad action spectrum [3].

Depending on the structure, physico-chemical and biological properties, the IFN are divided into two types: type I or viral IFN and type II or immune IFN. IFN of type I are synthesized by virtually all cells of the body, including non-immunocompetent and poorly differentiated cells. In contrast, IFN of type II can be generated by immunocompetent cells only during their stimulation [4].

IFN of type I are considered to be the first line of defense against viral infection. The main role of this type of IFN is to limit viral spread during the first days of infection. This time is enough for the formation of a strong adaptive immune response to infection, for which the IFN of type II, IFN-γ, is responsible. Binding of IFN-α/β (IFN of type I) or IFN-γ with its specific cell receptors alters the transcriptional and translational properties of the cells, which leads to the formation of antiviral condition in the body [5]. Table shows the IFN preparations used in medical practice for diseases of HV nature.

Despite a number of positive effects of IFN medicines, they also have significant drawbacks that greatly limit their use. In particular, during the treatment of herpes infection when there is a need for prolonged use of interferon , in the body there are formed anti-interferon antibodies that neutralize IFN molecules which arrive with the further consumption. [6] If overdosed on IFN, there is observed a large number of side effects [7]. It shall be also noted that long-term courses of treatment with IFN hitherto remain extremely expensive and therefore are not affordable for everyone.

A number of advantages over exogenous IFN is gained by self-IFN that does not have antigenicity and is produced in the body by means of induction – extracellular activation of relevant genes. This process is carried out from outside of the cell by a variety of inducers. It is found out that with no induction, the level of the messenger RNA (mRNA) of IFN genes in producing cells is so low that it has no definition. But an hour after the start of induction there are produced about 2000 of mRNA transcripts per cell. Note that the specified process is lengthy: the level of IFN mRNA reaches a peak in 6-12 hours after induction, and then rapidly decreases [8, 9]. Such a pulse manifestation of mRNA synthesis leads to short-term IFN production. Thus, it is induction which should be considered a key step in the biosynthesis of IFN and IFN inducers – the main factors that cause the production of IFN. While synthesis of self-IFN is controlled by repressing proteins and does not reach a level that is capable of negative effects on the body [10]. In the case of viral infection, antiviral action of many IFN inducers is caused not only by their

ability of interferongenesis, but also other mechanisms. This, in its turn, allows us to consider IFN inducers as a separate class of antiviral compounds of nonspecific action.

We have shown antiviral effect of interferon-inducing complex of yeast RNA tilorone on the model of HV-infection, in particular, revealed a general depressant effect of a specified complex on the run of HV infection *in vivo*, determined the ability of the complex to maintain a high level of performance of cytokine status of animals, and for the first time proved that the antiviral effect of complex of yeast RNA tilorone on HV infection is not limited to stimulation of nonspecific protection of the body, but also manifested in direct depressant effects of this compound on the reproduction of HSV-1 *in vitro* [11, 12, 13]. Table shows the preparation of INF inducers, used in medical practice for the treatment of HV-diseases.

The third group of preparations used for immunotherapy of herpesvirus infections are immunomodulators. These include drugs that can modify the immune response due to direct effects on immunocompetent cells, or indirectly – through changes in biological reactions of the body. In modern medical practice in the capacity of immunomodulators there is used a variety of drugs – the structural components and metabolites of microorganisms, amino acid preparations, cytokines, drugs of plant and animal origin, synthetic compounds, minerals, and some combinations of drugs [14]. Immunomodulators, used today for the treatment of herpes infections in Ukraine, are shown in table.

Table

Commercial preparations of interferons, interferon inducers and immunomodulators

Preparation	Active substance	Effect on herpesviruses
Preparations of interferons		
Berofor	Recombinant IFN-α-2c	HSV-1,2, HHV-8, HHV-3, HHV-4
Betaferon	Recombinant IFN beta-1b	HHV-6
Interferon beta	Human fibroblast β-IFN	HSV-1,2, HHV-3

Ehiferon	Human leukocyte α-IFN	HSV-2, HHV-3, HHV-4
Intron-A	Recombinant interferon (IFN-α-2b)	HSV-1,2
Reaferon	Recombinant α2-IFN)	HSV-1,2
Preparations of interferon inducers		
Amiksyn	dihydrochloride 2,7-bis-[2 (diethylamine)-ethoxy]-fluorene-9-on, tilorone	HSV-1,2, HHV-4, HHV-5, HHV-6
Amizon	N-methyl-4-benzylcarbamidepyridine iodide	HV
Arbidol	Ethyl ether methylfeniltiomethyl hydroxybromindol of carboxylic acid	HV
Laryfan	Double helix RNA	HSV-1,2, HHV-3, HHV-4
Mehasyn	Hosipol derivatives (Hosipol-b – amino ethyl sulfuric acid sodium)	HV
Neovir	Oksodihydroacridinil-sodium acetate	HSV-1,2, HHV-3, HHV-5
Poludan	Biosynthetic polirybonucleotide complex of poliryboadenil and polirybouridilic acids	HSV-1,2, HHV-3
Rydostyn	Rybonucleat sodium	HSV-1,2, HHV-3, HHV-4
Savrats	Natural low molecular weight compounds, hosipol derivatives	HSV-1,2
Cyclopheron	Meglumine acridonatsetat	HSV-1,2, HHV-5
Immunomodulators		
Aloferon	Oligopeptides of 13 amino acids	HSV-1,2
Alpizaryn	Tetrahydroxygluco-piranozilxanten	HSV-1,2, HHV-3, HHV-4, HHV-5
Halavit	Phthalhydrozid derivative	HSV-1,2
Hroprynosyn	Inosine pranobeks	HSV-1,2, HHV-5
Isoprinosin	Inosine pranobeks	HSV-1,2, HHV-3, HHV-4, HHV-5
Immunomax	Sour peptidoglucan	HSV-1,2
Imunofan	Arinil-alpha-aspartyl-lizil-valil-tyrosyl-arginine	HV
Licopid	Glucozaminilmuramil-dipeptide	HV
Polyoxidonium	Poliethylenpiperazyn derivative	HSV-1,2

Note: HSV-1,2 – herpes simplex virus of type I and II, HHV-3 – human herpes virus type 3 or varicella zoster virus, HHV-4 – human herpes virus type 4 or Epstein-Barr virus, HHV-5 – human herpes virus type 5 or cytomegalovirus, HHV-6 – human herpes virus type 6, HHV-8 – human herpes virus of type 8 or Kaposi's sarcoma.

The disadvantage of using immunomodulators in herpesvirus infections is the issue of guaranteed changes of immune response in the right direction. At present, this problem has no practical solution. The use of immunomodulators in case of acute viral infection leads to the activation of T-killer cells, which can lead to fatal consequences due to destruction of the tissues, infected by the virus. Given the fact that patients with severe and recurrent herpetic disease have specific immunodeficiency, the possibility of modification in their immune response to antigens of persistent and new strains of herpesviruses is greatly limited or nonexistent.

Conclusions. Despite the large number of antiherpethetical preparations, only a small number of them is used in Ukraine for the treatment of herpetic diseases. This is due to significant shortcomings of these drugs and their high cost. Assessment of current state of treatment of herpesvirus infections suggests that the main direction of research in this regard is the search and development of preparations that would not only have antiviral effect,but also be immunostimulating and, in particular, interferon inducing. Inducers of IFN, as outlined above, fall into such preparations.

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