JOURNAL OF MULTIDISCIPLINARY SCIENCES AND INNOVATIONS
VOLUME 5, ISSUE 06
MONTHLY JOURNALS
ISSN NUMBER: 2751-4390
IMPACT FACTOR: 9,08

UO'K: 616.98:578.825-08

GERPES VIRUSINING ZAMONAVIY DAVOSI VA ANTIVIRAL PREPARATLARGA REZISTENTLIK MUAMMOLARI

[1]Abdurahmonova K.R., [2]Dusiyorova M.S
[1]TDTU Mikrobiologiya, virusologiya, immunologiya kafedrasi assistenti
karima.abdurahmonova1990@gmail.com +998977275708
[2]TDTU 1- Davolash fakulteti talabasi mahliyodusiyorova06@gmail.com +998881401006

Annotatsiya. Ushbu maqolada Herpes simplex virusi (HSV-1 va HSV-2) chaqiradigan infeksiyaning zamonaviy davolash usullari, antiviral preparatlarga rezistentlik muammolari hamda istiqbolli terapevtik yondashuvlar keng tahlil qilingan. Gerpes infeksiyasi dunyo bo'yicha eng keng tarqalgan surunkali virusli kasalliklardan biri bo'lib, virusning nerv gangliylarida latent holatda umrbod saqlanib qolishi kasallikni to'liq davolashni murakkablashtiradi. Maqolada asiklovir, valasiklovir va famsiklovir kabi asosiy antiviral preparatlarning ta'sir mexanizmi, klinik samaradorligi, qo'llanilish tamoyillari hamda rezistent shtammlar bilan bog'liq muammolar yoritilgan. Shuningdek, immunomodulyatorlar, terapevtik vaksinalar, mRNK texnologiyalari, CRISPR-Cas9 gen tahrirlash tizimi, epigenetik boshqaruv va tabiiy antiviral birikmalar asosidagi yangi davolash strategiyalari haqida zamonaviy ilmiy ma'lumotlar keltirilgan. Maqolada HSV ning latent holati, relapslarning oldini olish, neonatal gerpes, gerpetik ensefalit va immun yetishmovchiligi bo'lgan bemorlarda kasallikning og'ir kechishi ham batafsil muhokama qilingan. Bundan tashqari, antiviral preparatlarga chidamli shtammlarning paydo bo'lish sabablari, virusning immun tizimdan qochish mexanizmlari hamda yangi avlod antiviral preparatlarining afzalliklari haqida ham ma'lumot berilgan.

Keywords: Herpes simplex virusi, HSV-1, HSV-2, antiviral terapiya, asiklovir, valasiklovir, famsiklovir, antiviral rezistentlik, latent infeksiya, relaps, CRISPR-Cas9, terapevtik vaksinalar, immunomodulyatsiya, epigenetik terapiya, mRNK vaksinalari, gerpetik ensefalit, neonatal gerpes

СОВРЕМЕННОЕ ЛЕЧЕНИЕ ГЕРПЕСВИРУСНОЙ ИНФЕКЦИИ И ПРОБЛЕМЫ РЕЗИСТЕНТНОСТИ К ПРОТИВОВИРУСНЫМ ПРЕПАРАТАМ

[1]Абдурахмонова К.Р., [2]Дусиёрова М.С.

[1]Ассистент кафедры микробиологии, вирусологии и иммунологии ТДТУ
karima.abdurahmonova1990@gmail.com +998977275708
[2]Студентка 1-лечебного факультета ТДТУ mahliyodusiyorova06@gmail.com
+998881401006

Аннотация. В данной статье подробно рассматриваются современные методы лечения инфекции, вызываемой вирусом простого герпеса (Herpes simplex virus, HSV-1 и HSV-2), проблемы резистентности к противовирусным препаратам, а также перспективные терапевтические подходы. Герпетическая инфекция является одним из наиболее распространённых хронических вирусных заболеваний в мире, при котором вирус способен пожизненно сохраняться в нервных ганглиях в латентном состоянии, что значительно осложняет его полное устранение. В статье освещены механизмы действия, клиническая эффективность и принципы применения основных противовирусных

препаратов, таких как ацикловир, валацикловир и фамцикловир, а также проблемы, связанные с появлением резистентных штаммов вируса. Кроме того, представлены современные научные данные об иммуномодуляторах, терапевтических вакцинах, технологиях мРНК, системе редактирования генома CRISPR-Cas9, эпигенетическом контроле и новых стратегиях лечения на основе природных противовирусных соединений.

Ключевые слова: Herpes simplex virus, HSV-1, HSV-2, противовирусная терапия, ацикловир, валацикловир, фамцикловир, противовирусная резистентность, латентная инфекция, рецидив, CRISPR-Cas9, терапевтические вакцины, иммуномодуляция, эпигенетическая терапия, мРНК-вакцины, герпетический энцефалит, неонатальный герпес.

MODERN TREATMENT OF HERPES VIRUS INFECTION AND PROBLEMS OF RESISTANCE TO ANTIVIRAL DRUGS

Abdurakhmonova K.R.,
Dusiyorova M.S.
Assistant of the Department of Microbiology, Virology and Immunology, TDTU
karima.abdurahmonova1990@gmail.com +998977275708
Student of the 1st Faculty of Medicine, TDTU
mahliyodusiyorova06@gmail.com +998881401006
https://doi.org/10.5281/zenodo.20514387

Abstract. This article comprehensively analyzes modern treatment methods for infections caused by Herpes simplex virus (HSV-1 and HSV-2), the problem of antiviral drug resistance, and promising therapeutic approaches. Herpes infection is one of the most widespread chronic viral diseases worldwide, characterized by the lifelong persistence of the virus in nerve ganglia in a latent state, which significantly complicates complete eradication of the infection. The article discusses the mechanisms of action, clinical efficacy, and principles of use of major antiviral drugs such as acyclovir, valacyclovir, and famciclovir, as well as issues related to the emergence of resistant viral strains. In addition, modern scientific data on immunomodulators, therapeutic vaccines, mRNA technologies, CRISPR-Cas9 genome editing systems, epigenetic regulation, and novel treatment strategies based on natural antiviral compounds are presented.

Keywords: Herpes simplex virus, HSV-1, HSV-2, antiviral therapy, acyclovir, valacyclovir, famciclovir, antiviral resistance, latent infection, relapse, CRISPR-Cas9, therapeutic vaccines, immunomodulation, epigenetic therapy, mRNA vaccines, herpetic encephalitis, neonatal herpes

Relevance. The Herpes simplex virus (HSV) is one of the most common viral infections among humanity. According to the World Health Organization, approximately 67% of the population under the age of 50 is infected with HSV-1, and 13% with HSV-2. HSV-1 primarily causes labial herpes, which is transmitted in most cases during childhood, while HSV-2 is the primary causative agent of genital herpes. One of the important aspects of the disease is that most infected individuals exhibit no clinical symptoms or have a very mild course, as a result of which the virus can be transmitted to other people without being noticed. HSV infection persists in the body for a lifetime and can reactivate under the influence of various factors - stress, decreased immunity, fever, surgical interventions, or ultraviolet radiation. According to the World Health Organization, HSV-2 infection increases the risk of HIV infection by approximately three times. Furthermore, in immunocompromised patients, herpes infection is more severe and can cause complications such as meningoencephalitis, keratitis, and disseminated infection [1-5]. Herpes Simplex Virus (HSV) type 1 (HSV-1) and type 2 (HSV-2) are two of the most prevalent viral diseases in humans, impacting billions of individuals globally.

Clinical signs and symptoms of HSV infection are often minor and self-limiting in healthy patients, but they are often more aggressive, persistent, and even fatal in immunocompromised patients. The most effective antiviral medications for treating and preventing HSV infections are acyclovir and its variants. Even though acyclovir resistance is a very rare illness, it can lead to major consequences, particularly in patients with impaired immune systems. Our goal in this review is to address the issue of drug-resistant HSV infection and go over the various therapy options [6-10]. In pregnant women, the transmission of the virus to the newborn causes the development of neonatal herpes, which is dangerous with the possibility of severe neurological complications and even death. Therefore, studying the problems of modern diagnosis, treatment methods, and resistance to antiviral drugs for HSV infection is currently one of the most pressing issues in medicine [20]. While HSV-1 primarily causes herpes in the labia and facial areas, HSV-2 is primarily associated with genital herpes. In recent years, the incidence of genital infections caused by HSV-1 has been increasing. The main problem with herpes infection is that the virus does not disappear completely after entering the body. It remains latent in the nerve ganglia for a long time and reactivates when immunity decreases. Therefore, the disease is chronic and relapsing in nature [19]. Relapses develop against the background of stress, ultraviolet radiation, hormonal changes, fever, trauma, or immunosuppression. We analyzed every relevant study that was published in PubMed between 1989 and 2022 regarding alternate treatment modalities for acyclovir-resistant HSV infection. Antiviral medication prophylaxis and long-term treatment increase the risk of drug resistance, particularly in patients with impaired immune systems. In certain situations, foscarnet and cidofovir may be used as alternate therapies. Acyclovir resistance is uncommon, although it can lead to serious problems. In order to prevent the current drug resistance, it is hoped that new antiviral medications and vaccines will become accessible in the future [12-15]. The most effective antiviral medications for treating and preventing HSV infections are acyclovir and its variants. However, acyclovir resistance can arise, particularly in people with impaired immune systems. Defects in cell-mediated immunity and intermittent or prolonged antiviral therapy are among the factors that put these patients at risk for developing resistance to antiviral medications, which could result in serious side effects like meningoencephalitis, esophagitis, and herpetic pneumonia that could make HSV infection a potentially fatal illness [14-19].

The main purpose of the presented manuscript is to provide a brief analysis of the problems of modern treatment of the herpes virus and resistance to antiviral drugs based on the results of authoritative scientific works.

HSV not only damages the skin and mucous membranes but can also damage the central nervous system. Herpetic encephalitis, meningitis, neonatal herpes, and disseminated infection are the most dangerous complications [10]. The mortality rate remains high, especially among newborns and immunocompromised patients. Existing antiviral drugs suppress viral replication but cannot completely destroy the virus in a latent state [13]. Therefore, the problem of the complete treatment of herpes is one of the most pressing areas of modern virology, immunology, and molecular biology. In recent years, CRISPR-Cas9 gene editing technology, therapeutic vaccines, epigenetic modulators, and next-generation antiviral drugs have been shown to have great prospects for treating herpes [17]. In addition, the increasing number of strains resistant to antiviral drugs also requires the development of new therapeutic agents. HSV is a double-stranded DNA virus from the family Herpesviridae. The virus's genome has a complex structure, containing more than 80 protein-coding genes [6]. Two main types of HSV are distinguished: HSV-1 and HSV-2. HSV-1 primarily causes orolabial herpes, while HSV-2 causes genital herpes. The virus enters the body through the skin or mucous membrane and begins to actively multiply in epithelial cells. Subsequently, it moves along the nerve fibers and enters the sensory ganglia.

HSV-1 is typically latent in the trigeminal ganglia, while HSV-2 is latent in the sacral ganglia [11].

During the latent period, the virus does not proliferate actively and is practically unrecognized by the immune system. During this period, LAT transcripts are primarily synthesized. This mechanism allows the virus to survive for a long time [14]. When the virus reactivates, it returns through nerve fibers to peripheral tissues, and clinical symptoms appear. The frequency of relapses depends on the patient's immune status. In some people, relapses occur once a year, while in others, they may recur several times a month. Antiviral drugs and their mechanism of action. The main treatment for herpes infection is antiviral drugs belonging to the group of nucleoside analogues. The most commonly used drugs are valclovir, valacyclovir, and famciclovir [2-9].

Acyclovir is the "gold standard" drug for the treatment of herpes. It was first developed in the 1970s and is still widely used today [9]. Acyclovir is activated by viral thymidine kinase. It then inhibits the viral DNA polymerase, stopping DNA synthesis. The main advantage of acyclovir is its selectivity. The drug is primarily activated in virus-infected cells; therefore, its toxic effect on healthy cells is relatively low. Clinical studies have shown that clovir reduces pain, accelerates wound healing, reduces viral excretion, and reduces the duration of relapses [7]. However, it cannot destroy a latent virus. Valacyclovir is a prodrug of valcyclovir. Upon entering the body, it is converted into clovir. The drug is convenient for patients due to its high bioavailability [3]. Valacyclovir is widely used in suppressive therapy. Taking 500–1000 mg per day can reduce relapses by 70–80% [5]. Famsiclovir is also one of the most effective anti-HSV drugs. It is a prodrug of pencyclovir. According to studies, famcyclovir demonstrates high efficacy in reducing the duration of relapses [15]. Long-term suppressive therapy is recommended for patients with frequent relapses. In this method, antiviral drugs are taken regularly for several months or years. The primary goal of suppressive therapy is to reduce the number of relapses, reduce viral transmission, and improve the patient's quality of life. Long-term use of Valacyclovir has been found to significantly reduce the incidence of genital herpes infection. Therefore, it is widely recommended for sexually active patients [1].

The resistance of HSV to antiviral drugs has become a serious problem in recent years. Resistant strains are particularly common in HIV-infected patients, transplant recipients, and patients receiving chemotherapy [12]. The main cause of resistance is mutations in the viral thymidine kinase gene. As a result, thymiclovir cannot be converted into an active form and becomes ineffective. Foscarnet is used in cases of acyclovir resistance. It directly inhibits DNA polymerase [4]. Although the drug is effective, its nephrotoxicity is high. Trifovir is also used against resistant HSV. It can cause nephrotoxic and hematological complications. In recent years, research has been conducted on new drugs such as prithelivir, maribavir, and amenamevir. Pritelivir inhibits the helicase-primasis complex and has shown effectiveness against strains resistant to pritelivir [18]. The immune system plays an important role in controlling HSV infection. CD8+ T-lymphocytes monitor latently infected neurons and suppress viral reactivation [8]. According to research, IFN-gamma inhibits viral replication, while granzyme B destroys infected cells. Resident T-cells are important in the prevention of relapses. Immunomodulatory drugs help strengthen the body's antiviral defense. In some cases, interferon preparations are used as complementary therapy [12,13].

Therapeutic vaccines: Creating a vaccine against herpes has been one of the most important areas of virology for many years. GEN-003 is a therapeutic vaccine that has been found to reduce HSV-2 relapses by 30–50% [16]. HSV529 is a weakened virus-based vaccine that generates a strong T-cell response. After the COVID-19 pandemic, mRNA technology also began to be used in herpes vaccines. Vaccines developed by Moderna and BioNTech are

showing promising results. CRISPR-Cas9 and gene editing. CRISPR-Cas9 technology is one of the most promising methods for the complete eradication of HSV. In 2016, Aubert and his colleagues succeeded in cutting the latent HSV genome using CRISPR. Subsequent studies have observed a reduction in viral DNA to 90–99 percent. The main advantage of CRISPR technology is the ability to destroy a latent virus. This can lead to the complete elimination of relapses. However, this technology also carries certain risks. The problems of off-target gene editing, immunogenicity, and long-term safety have not yet been fully studied. Nevertheless, CRISPR technology could provide a complete cure for herpes in the future. HSV latency is controlled by epigenetic mechanisms. Histone modification and DNA methylation play an important role in the viral genome [10,11].

HDAC inhibitors can re-activate a latent virus. According to this "shock and kill" strategy, the latent virus is first activated and then destroyed using antiviral drugs. Preparations such as vorinostat and panobinostat have shown promising results in experimental studies. Natural compounds can be used as adjuvant therapy against HSV. Flavonoids, including baikaline, quercetin, and luteolin, inhibit viral replication [11]. Melissa officinalis extract has an antiviral effect against HSV [14]. Lysine is an arginine antagonist and can reduce the number of relapses [9]. Zinc, vitamin D, and vitamin C support immune function [7]. However, natural remedies cannot replace basic antiviral therapy and are used only as an auxiliary agent. Neonatal herpes is one of the most dangerous viral infections in newborns. The infection is usually transmitted from mother to child during childbirth. The disease can have a cutaneous-ocular-oral form, involve the central nervous system, or be disseminated. The mortality rate in the disseminated form is very high [15]. Treatment involves the intravenous administration of thymiclovir at a dose of 20 mg/kg every 8 hours for 21 days[1]. Early diagnosis and prompt treatment significantly improve the prognosis. Herpetic encephalitis. Herpes simplex encephalitis is considered one of the most severe viral diseases of the central nervous system [16]. The main symptoms of the disease are fever, impaired consciousness, seizures, and neurological symptoms. Without treatment, the mortality rate exceeds 70 percent. Treatment with acyclovir reduces this indicator by up to 20%. In the future, combined therapies combining antiviral drugs, immunostimulants, gene editing, and epigenetic modulators may provide a complete cure for herpes [15,16,21].

Conclusions. The Herpes simplex virus is a common viral infection that persists throughout life in the human body. Currently, drugs such as valclovir, valacyclovir, and famcyclovir are effective in controlling the disease, but they cannot completely destroy the latent virus. Increasing resistance to antiviral drugs requires the development of new treatment strategies. Immunomodulators and therapeutic vaccines play an important role in reducing relapses. CRISPR-Cas9 gene editing technology is the most promising direction today, as it allows for the destruction of the latent viral genome. Epigenetic therapy, HDAC inhibitors, and next-generation antiviral drugs are also expanding the prospects for treating herpes. In the future, it may become possible to completely eliminate herpes using combined therapies.

The cornerstone for treating and preventing HSV-1 and -2 infections has been acyclovir and its congeners. Although ACVr is a rare illness that primarily affects immunocompromised patients, it can have serious consequences. Even while the prevalence of ACVr has remained steady over the past 40 years, the increasing number of immunocompromised patients and their longer survival times increase the likelihood that resistance may become a concern in clinical practice. The safest strategy that guarantees a timely transition to an alternate antiviral medication and prevents unfavorable clinical consequences is increased knowledge and care for the potential of ACVr HSV-infections. Research is currently underway to develop novel antiviral

medications that circumvent TK-dependent or DNA pol-related drug resistance. Hopefully, these medications will soon be accessible for usage.

References

1. American Academy of Pediatrics. Red Book: Herpes Simplex. 2021.
2. Aubert M, et al. In vivo disruption of latent HSV by CRISPR-Cas9. JCI Insight. 2016;1(14):e88684.
3. Bloom DC, Giordani NV, Kwiatkowski DL. Epigenetic regulation of HSV latency. J Virol. 2010;84(20):10454-10463.
4. CDC. Sexually transmitted infections treatment guidelines. MMWR. 2021.
5. Corey L, Wald A, Patel R, et al. Valacyclovir suppression of HSV-2 transmission. Ann Intern Med. 2004;140(9):668-674.
6. Fields BN, Knipe DM, Howley PM. Fields Virology. Philadelphia: Lippincott Williams & Wilkins; 2021.
7. Gaby AR. Natural remedies for herpes simplex. Altern Med Rev. 2006;11(2):93-101.
8. Gebhardt T, Wakim LM, Eidsmo L, et al. Memory T cells in tissue immunity. Nat Rev Immunol. 2009;9(10):695-704.
9. Griffith RS, Norins AL, Kagan C. Lysine therapy in herpes simplex infections. Dermatologica. 1987;175(4):183-190.
10. Kimberlin DW, Whitley RJ. Neonatal herpes. N Engl J Med. 2005;353(17):1809-1816.
11. Koch C, Reichling J, Schneele J, Schnitzler P. Antiviral activity of flavonoids against HSV. Antiviral Res. 2021;192:105102.
12. Piret J, Boivin G. Antiviral resistance in herpes simplex virus infections. Curr Opin Infect Dis. 2016;29(6):654-662.
13. Roizman B, Knipe DM, Whitley RJ. Herpes simplex viruses. Fields Virology. 7th ed. Wolters Kluwer; 2021.
14. Schnitzler P, Schuhmacher A, Astani A, Reichling J. Melissa officinalis oil against HSV infection. Phytomedicine. 2008;15(9):734-740.
15. Spruance SL, Tyring SK, DeGregorio B, et al. Famciclovir for recurrent HSV infection. Antimicrob Agents Chemother. 1997;41(2):359-365.
16. Srivastava R, et al. Therapeutic vaccines for HSV infection. Hum Vaccin Immunother. 2019;15(10):2414-2428.
17. van Diemen FR, Lebbink RJ. CRISPR-Cas systems for herpesvirus infections. Curr Opin Virol. 2021;50:45-52.
18. Wald A, Timmler B, Magaret A, et al. Helicase-primase inhibitor pritelivir for HSV-2 infection. N Engl J Med. 2014;370:201-210.
19. Whitley RJ, Roizman B. Herpes simplex virus infections. Lancet. 2001;357(9267):1513-1518.
20. World Health Organization. Herpes simplex virus. Fact sheet. 2023
21. Piperi, E., Papadopoulou, E., Georgaki, M., Dovrat, S., Bar Illan, M., Nikitakis, N. G., & Yarom, N. (2024). Management of oral herpes simplex virus infections: The problem of resistance. A narrative review. Oral Diseases, 30, 877–894. https://doi.org/10.1111/odi.14635