REVIEW

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Combination drug therapy as a strategy to improve the efficacy and safety of treatment of herpes simplex virus infections: potential risks and prospects

Valeriya L. Andronova ✉, Georgy A. Galegov

The N.F. Gamaleya Research Center of Epidemiology and Microbiology of the Russian Ministry of Health, 123098, Moscow, Russia

Abstract
Herpes simplex viruses (HSV) are extremely widespread pathogens that cause human infections of varying severity, from mild orofacial ulcerations of the skin and mucous membranes to life-threatening encephalitis and severe generalized forms of infection or recurrent herpetic corneal lesions leading to blindness. Standard treatment with acyclovir, penciclovir, or the corresponding prodrugs valacyclovir and famciclovir is usually sufficient to stop recurrent HSV infections. However, immunocompromised patients are of particular concern and often require long-term antiviral therapy. In such conditions, the risk of developing drug resistance, often cross-resistance increases significantly, since all basic antiherpetic drugs have a similar mechanism of action and affect the same drug target – viral DNA polymerase (DNA-pol). With the development of drug resistance, the effectiveness of treatment decreases, and it becomes necessary to switch to second-line drugs with severe side effects. Thus, it is necessary to develop new alternative treatment options. The creation of drugs aimed at a biotarget different from DNA-pol eliminates the risk of cross-resistance to acyclovir and related drugs, and their use in combination with traditional antiherpetic drugs can prevent or slow down the development of drug resistance in the virus. When combining drugs that affect the pathogen in different ways, it is important to maintain the therapeutic effect with the use of lower doses due to the synergistic nature of the interaction, which reduces the likelihood of developing unwanted side effects of drugs. The review presents current data on the state and possible prospects for the development of combination therapy for HSV infections, obtained as a result of searching the literature related to anti-herpetical therapy using the PubMed, Medline databases, RSCI, the international registry of clinical trials of the US National Institutes of Health.

Keywords: *herpes simplex virus; antiviral drugs; drug interactions; drug combination therapy; antiviral drug resistance; review*

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НАУЧНЫЙ ОБЗОР
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Комбинированная лекарственная терапия как стратегия повышения эффективности и безопасности лечения инфекций вируса простого герпеса: возможные риски и перспективы

Андронова В.Л.✉, Галегов Г.А.

ФГБУ «Национальный исследовательский центр эпидемиологии и микробиологии имени почетного академика Н.Ф. Гамалеи» Минздрава России, 123098, г. Москва, Россия

Резюме.
Вирусы простого герпеса (ВПГ) – чрезвычайно широко распространенные патогены, вызывающие у человека заболевания разной степени тяжести: от легких орофациальных изъязвлений кожи и слизистых оболочек до потенциально опасных для жизни энцефалита и тяжелых генерализованных форм инфекции или рецидивирующих герпетических поражений роговицы, приводящих к слепоте. Обычно для купирования рецидива инфекций ВПГ достаточно стандартного лечения, включающего ацикловир, пенцикловир или соответствующие пролекарства – валацикловир и фамцикловир. Однако пациенты со сниженным иммунным статусом вызывают особую озабоченность. Им часто требуется проведение длительной противовирусной терапии. В таких условиях значительно увеличивается риск развития у вируса лекарственной устойчивости, часто носящей перекрестный характер, т.к. все базовые противогерпетические препараты имеют схожий механизм действия и поражают одну лекарственную мишень – вирусную ДНК-полимеразу (ДНК-pol). При развитии лекарственной резистентности снижается эффективность лечения и возникает необходимость перехода к препаратам второго ряда с тяжелыми побочными эффектами. Таким образом, существует необходимость разработки новых альтернативных путей лечения. Создание препаратов, нацеленных на отличную от ДНК-pol биомишень, исключает риск перекрестной резистентности к ацикловиру и родственным препаратам, а их использование в комбинации с традиционными противогерпетическими препаратами может предотвратить или замедлить развитие лекарственной резистентности у вируса. Важно, что при комбинировании препаратов, воздействующих на инфекционный агент различными путями, терапевтический эффект может сохраняться при использовании более низких доз лекарственных средств благодаря синергическому характеру взаимодействия, что снижает вероятность развития нежелательных побочных эффектов лекарств. В обзоре представлены актуальные данные о состоянии и возможных перспективах развития комбинированной терапии инфекций, вызываемых ВПГ, полученные в результате проведения поиска литературы, связанной с антигерпесвирусной терапией, с использованием баз данных PubMed, Medline, РИНЦ, международного реестра клинических исследований Национального института здоровья США.

Ключевые слова: *вирус герпеса простого; противовирусные препараты; взаимодействие лекарств; комбинированная терапия; устойчивость к противовирусным препаратам; обзор*

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Финансирование. Авторы заявляют об отсутствии внешнего финансирования при проведении исследования.

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Introduction

Clinical experience of combined use of two or more antiviral drugs shows that the synergistic (mutually reinforcing) or additive (summation) nature of their interaction opens the possibility of increasing the effectiveness of therapy when using drugs in suboptimal doses. Under such conditions, toxicity and the risk of harmful side effects are reduced. The development of virus drug resistance, which complicates treatment, can also be delayed or even prevented by combination therapy, since the development of resistance to several drugs at the same time is less likely. The combined use of antiviral drugs with different mechanisms of action, which provides a significant reduction in viral load and consequently in disease severity and mortality, is the gold standard for the treatment of severe chronic viral diseases caused by HIV-1 [1] and hepatitis C virus [2]. Combination therapy is the optimal strategy for effective treatment of influenza infection [3], the possibilities of introducing new combinations of anti-influenza drugs into clinical practice are being actively investigated [Phase II, III clinical trials (ClinicalTrials.gov Identifiers: NCT05170009, NCT04712539, enrollment of participants). New approaches to combination therapy against COVID-19 [4], as well as against Ebola virus [5] and Zika virus are being developed [6].

Herpes virus type 5 (human cytomegalovirus, CMV) infections are a common complication after organ transplantation, increasing the risk of graft loss and death, as well as a cause of congenital infections leading to sensorineural hearing loss and neurological disorders in children. After the introduction of two drugs for the treatment of CMV infection, the CMV protein kinase inhibitor pUL97 (maribavir, MBV, Livtencity, Takeda, Japan)) and inhibitor pUL56, which is part of the CMV terminase complex (letermovir, LMV, Prevymis, Merck, USA), their possible combinations with traditional anti-herpetic agents, viral DNA polymerase (DNA-pol) inhibitors, began to be actively studied. Preclinical *in vitro* studies have shown that the combined use of MBV with ganciclovir (GCV), cidofovir (CDV) and LMV results in additive effects [7], although, according to other data, MBV and LMV in combination provide synergistic enhancement of the anti-CMV effect *in vitro* [8]. However, MBV interacts antagonistically with GCV because it inhibits pUL97, an enzyme required for phosphorylation of GCV to form monophosphate (step 1 of HSV activation) [7]. When LMV is combined with GCV and CDV, additive effects are observed, while weak synergistic effects are observed with foscarnet (FOS) [9]. (The formulas of the compounds mentioned above are given in **Table 1 of the Annex**).

The aim of the review is to assess the status and possible prospects for the development of combination therapy for infections caused by HSV.

Clinical significance of herpes simplex virus-associated infections

Herpes simplex virus (HSV) (*Herpesviridae* family) is one of the most common pathogens worldwide. According to the information bulletin of the World Health Organization (WHO) dated December 11, 2024, about 3.8 billion people under the age of 50 years are seropositive to HSV type 1 (HSV-1) and another 520 million people in the age group from 15 to 49 years are carriers of HSV type 2 (HSV-2). Thus, the prevalence of these viruses in these age categories has reached 64 and 13% respectively and, according to WHO experts, it is higher in the older age group[1].

After primary infection, HSV establishes a lifelong latent infection in neuronal ganglia and periodically reactivates. Clinical manifestations during relapse are observed in only 5–15% of cases [10], but the extremely high level of infection in the population results in a huge number of people suffering from HSV-related diseases, including orofacial lesions, herpetic stomatitis, herpetic eczema and ocular diseases (corneal damage can subsequently lead to irreversible decrease in visual acuity and blindness). In 2020 alone, about 205 million people aged 15–49 years had a manifest episode of genital herpes (5.3% of the total number of carriers, WHO estimates). Furthermore, infection with HSV-2, with which most cases of genital herpes are associated, increases the risk of HIV infection and transmission[1]. Neonatal herpes, visceral and disseminated infections, meningitis and herpetic encephalitis are rare diseases that occur mainly in neonates or immunocompromised individuals, including cancer patients and transplant recipients, but can result in neurological disability or death [11]. There seems to be an association between HSV-1 infection and Alzheimer's disease [12]. Thus, infections caused by HSV not only reduce the quality of life of virus carriers, but may have a severe course with an unfavorable prognosis, especially in cases of ineffective therapeutic measures[1]. To date, there are no licensed prophylactic and therapeutic vaccines against HSV, despite enormous efforts to develop them.

Current etiotropic therapy of HSV infections and the problem of virus drug resistance

Acyclovir (ACV), its prodrug valacyclovir (L-valine ester of ACV, VACV), and famciclovir (FCV), the metabolic precursor of penciclovir (PCV)[1] are included in the group of first-line etiotropic drugs currently approved for the treatment of HSV infections [13]. Oral formulations of ACV, VACV and FCV are intended for the prevention and treatment of mild to moderate infections, while intravenous ACV is the drug of choice for severe visceral and disseminated forms of infection or CNS disease. Unfortunately, these drugs have limited efficacy because treatment should be started as early as possible, preferably in the prodromal period, and the recovery period is usually shortened by only 1–2 days for orofacial herpes and 3 days for genital herpes [14, 15].

ACV, PCV, as well as GCV belong to the class of guanosine nucleoside analogs. The selectivity of the antiviral activity of these compounds is due to their selective phosphorylation to the monophosphate form by herpetic thymidine kinase (TK, pUL23). After subsequent di- and triphosphorylation by cellular kinases, the corresponding triphosphates, acting as competitors of natural nucleotides, are incorporated into the growing viral DNA strand, which leads either to chain breakage or to a significant slowdown of synthesis, and affect the same bio-target – viral DNA-pol, inhibiting its function [13].

Stable maintenance of effective suppression of virus reproduction under the pressure of ongoing drug therapy prevents spontaneous mutations as a natural result of DNA-pol errors. However, if the suppressive effect of therapy is insufficient, virus replication continues when drugs are used in suboptimal doses (due to an error in the choice of dose and/or regimen or omission of drug administration, non-adherence to the treatment regimen or for other reasons). Under such conditions, the risk of drug resistance development increases due to the selection of pre-existing minor drug-resistant viral particles in viral populations under the selective pressure of the drug. In 95% of cases, the decrease in drug sensitivity of HSV to modified nucleoside drugs is associated with mutations in the viral TK and/or in 5% of cases in the target viral protein pUL30, the catalytic subunit of DNA-pol [16]. The ineffectiveness of current chemotherapeutic measures is often associated with the development of virus

[1] Herpes simplex virus. Fact sheet. 11 December 2024. Available at: https://www.who.int/ru/news-room/fact-sheets/detail/herpes-simplex-virus

drug resistance. It is important to emphasize that HSV strains resistant to ACV are in the vast majority of cases cross-resistant to other nucleoside analogs [17].

The prevalence of HSV infections with reduced sensitivity to ACV varies depending on the immunity status of the patient and does not exceed 1% in immunocompetent individuals [13], except for infections of immune-privileged sites, such as the cornea: in recurrent herpetic keratitis, resistant HSV isolates are isolated with a frequency of up to 6.4% of cases [18]. In contrast, the prevalence of ACV-resistant strains of HSV in immunocompromised patients is much higher, ranging from 2.5–10.9% in HIV-positive patients, cancer patients receiving myelosuppressive chemotherapy, and solid organ transplant recipients [13], and even higher rates of ACV resistance have been reported after allogeneic hematopoietic stem cell transplantation, ranging from 14 to 46.5% with a tendency to increase [19, 20]. The formation of resistant viral populations in these groups of patients at high risk of developing active HSV infection is facilitated by continuous prophylactic therapy required to block viral reactivation and prolonged drug treatment in case of disease relapse, usually with a severe course, necessary to maintain continuous suppression of viral reproduction. In patients with ACV-resistant herpetic lesions, ACV-resistant infection relapses after discontinuation of treatment within an average of 42.5 days (ClinicalTrials.gov Identifier NCT00000985) [21].

In cases where resistance to ACV/PCV is confirmed or suspected to correlate with the ineffectiveness of the current chemotherapy, a switch to a second-line drug – trisodium phosphonoformate pyrophosphate analog (foscarnet, FOS) is required, and in case of ineffectiveness of FOS, a nucleotide analog CDV can be recommended for alternative treatment [22]. It should be noted that FOS and CDV are nephrotoxic and have a number of severe side effects. Furthermore, these drugs are administered intravenously. For these reasons, patients require constant in-hospital monitoring [13].

FOS, mimicking pyrophosphate, directly binds to the γ-phosphate binding site of the incoming nucleotide in the active center of viral DNA-pol and disrupts its functioning by inhibiting the cleavage of pyrophosphate from nucleoside triphosphate (NTP) [13]. CDV contains a phosphonate moiety that bypasses the first phosphorylation step and is converted by cellular kinases to diphosphate, which competes with deoxycytidine triphosphate for incorporation into elongating DNA and reduces viral DNA-pol activity [13]. ACV/PCV-resistant strains of HSV retain sensitivity to FOS and CDV in most cases, as they do not require viral TK activation [17]. However, the biomimetic target of these drugs, as well as of modified nucleosides, is viral DNA-pol [13], which can lead to the emergence of multidrug-resistant HSV infections, resistant to ACV and FOS and/or CDV, as described in a number of publications [23, 24], but such mutants are found predominantly in immunocompromised patients after one drug is gradually replaced by another, rather than when they are used in combination [25, 26]. The emergence of such multidrug-resistant HSV infections necessitates the need for new classes of anti-herpetic drugs with alternative mechanisms of action and the combination of traditional and new drugs. (The formulas of the compounds mentioned in this section are given in **Tables 1 and 2 of the Annex**).

Types of drug interactions in the combined use of antiviral compounds. Possibilities of combined etiotropic therapy

In cases where monotherapy is ineffective, especially due to the development of virus drug resistance, regimens containing two or more agents may be useful both to increase the efficacy of the effect on viral infection and reduce the likelihood of undesirable side effects of the combined agents, and to reduce the risk of formation or rate of development of drug resistance. It is obvious that the combined use of drugs affecting different bio-targets and, therefore, not sharing common resistance patterns, significantly increases the genetic barrier to drug resistance (meaning the number and type of substitutions required to confer resistance), since several mutations are required for the virus to adapt to the inhibitory action of two antiviral drugs simultaneously. However, drug interactions should be studied beforehand, taking into account the fact that they may be either synergistic or additive or antagonistic in nature. In the latter case, higher doses of drugs are required to achieve in combination the same effect of compounds as when used separately [7].

The rational selection of drug combinations capable of potentiating the therapeutic efficacy of each other is based on an understanding of the mechanism of their action, which determines the potential for drug interactions. It is also necessary to take into account the factors that may affect the combined efficacy of combined drugs *in vivo* – route of administration, bioavailability, metabolic transformations, distribution in organs and tissues.

Drug combinations can be divided into three types

1. Combinations of antiviral agents acting on different bio-targets or non-competitive inhibitors binding to different sites of the same target can provide the best therapeutic effect with fewer side effects, since in such cases the combined compounds do not interfere with each other in binding to the target protein and are likely to interact synergistically, i.e. their combined antiviral effect will be greater than the sum of their individual effects.

2. Combinations of competitive inhibitors targeting the same site of the target protein are likely to interact additively, since their simultaneous binding to the target protein site is not possible, and the effect will be summed up by increasing the total number of inhibitory molecules.

3. Compounds that have antiviral activity may be combined with compounds that do not have such an effect on their own, but enhance the effect of the active component, for example, by influencing the rate of its metabolism (increasing the rate of formation of the active metabolite or slowing down the rate of inactivation of the compound), or increasing its bioavailability, etc.

Combined etiotropic therapy of HSV infections

First type of combinations. Two pairs of non-competitive DNA-pol inhibitors – ACV or PCV with FOS – are

examples of combinations of the first type. Their high synergistic activity against HSV-1 and HSV-2 was established in *in vitro* experiments [27]. However, there is currently only limited clinical experience with the use of PCV in combination with FOS, for example, for the treatment of encephalitis caused by HSV-1 [28, 29], or neonatal infection with HSV-2 resistant to ACV [30], since the use of such a tactic is possible only in patients in critical condition due to severe side effects of FOS, mainly nephrotoxicity, and also due to potential nephrotoxicity of ACV (acute kidney injury is registered in 8.7 and 8.6% of cases when taking ACV and VACV, respectively, and significantly more often in patients taking ACV or VACV simultaneously with non-steroidal anti-inflammatory drugs – in 10.5 and 19.4% of cases, respectively) [31]. Furthermore, there are known cases of exacerbation of herpetic infection when taking ACV together with FOS, as well as with CDV or GCV, despite the fact that all these drugs have anti-herpetic activity. In such cases, it is recommended to return to the use of ACV monotherapy as usual [32].

The efficacy of the combination of FOS and GCV against HSV-2 in *in vitro* experiments corresponded to the synergistic type, but when used in the model of herpetic infection in mice, its effect was reduced to additive [33]. This combination is recommended by the Infectious Diseases Society of America for the treatment of encephalitis caused by CMV [34], and also in reduced doses can be administered in case of CMV resistance to CDV [35], i.e. in especially severe cases when there is a threat to the patient's life. Taking into account the fact that FOS is nephrotoxic and GCV is almost completely excreted by the kidneys, it is necessary to carefully monitor the doses of these drugs and renal function during their simultaneous use to prevent a significant increase in the plasma concentrations of these compounds and to prevent the development of severe side effects [32]. The combination of GCV and FOS has not been investigated for the treatment of HSV infections under clinical conditions, apparently taking into account that the possible risk of developing severe side effects with its use exceeds the potential benefit.

Although combination therapy with CDV and GCV has been shown to be effective in the treatment of persistent multidrug-resistant HSV-1 infection (resistant to ACV and FOS) [36], the combined use of CDV, a drug with a high risk of nephrotoxicity, with other potentially nephrotoxic agents (ACV/VACV, GCV and FOS) is contraindicated and, according to recommendations, a patient can be switched from one of these agents to CDV only after 7 days of discontinuation of these agents[2].

Thus, the combined use of drugs of modified nucleosides or their prodrugs with second-line drugs is undesirable or even prohibited.

Second type of combinations. The purine-containing nucleosides ACV, PCV or GCV interact in combination only additively [27], which can be explained by the similarity of their mechanisms of action. The effect of binary combinations of ACV with thymidine analogs brivudin (BVDU) and trifluorothymidine (TFT) or BVDU and TFT has been similarly evaluated [37]. These compounds are also phosphorylated by viral TK – BVDU to mono- and diphosphate, and TFT to monophosphate, then to triphosphates by cellular kinases. The triphosphates of BVDU and TFT compete for binding to the DNA-pol nucleoside-binding site [38]. In view of the above, as well as taking into account the cross-drug resistance of the virus to these compounds, their combined use is inadvisable.

Combination therapy of ACV with vidarabine (Ara-A), a purine-containing DNA-pol inhibitor, was effective in the treatment of neonatal encephalitis caused by ACV-resistant HSV-1 [39]. However, due to severe side effects, Ara-A for intravenous administration has been withdrawn from production, and only the ointment dosage form is currently available. Thus, to date, the combination of these compounds in dosage forms intended for systemic administration is not relevant. (The formulas of the compounds mentioned for the first time in this subsection are given in **Table 3 of the Annex**).

Third type of combinations. It is possible to combine antiviral agents with drugs that themselves have little or no effect on viral replication, but significantly enhance the effect of the active component. For example, ribavirin, an inhibitor of the cellular enzyme inosine monophosphate dehydrogenase (IMPDH), is known as a broad-spectrum antiviral drug; however, it shows low activity against HSV-1 *in vitro* [40] and *in vivo* in experimental herpetic keratoconjunctivitis in rabbits, but it enhances the antiviral activity of purine nucleoside analogs ACV, PCV, GCV, etc. under the same experimental conditions [41]. The potentiation of antiviral effect is explained by the fact that in the monophosphate form ribavirin competes for binding to the natural substrate of IMPDH – inosine monophosphate (IMP) – and thus causes not only an increase in the pool of IMP (phosphate donor), as a result of which the phosphorylation of purine nucleosides is intensified, but also suppresses the activity of this enzyme, which leads to the depletion of intracellular pools of deoxyguanosine triphosphate, with which ACV, PCV and GCV in the form of triphosphates compete for binding to DNA-pol. This increases the efficiency of their incorporation into the growing DNA strand during replication [42].

The immunosuppressant mycophenolate mofetil (MPM) is a 2-morpholinoethyl ester of mycophenolic acid (MPA), as well as its prodrug. MPA on its own is practically inactive against HSV, but inhibits the activity of IMPDH, as it was shown in *in vitro* experiments, and has a significant potentiating effect on the activity of ACV, PCV and GCV [43]. MPM is used to prevent acute transplant rejection in patients after allogeneic kidney, heart and liver transplantation. At the same time, recurrences of herpetic infection may develop, and ACV, VACV, FCV or GCV are used to control them. However, we did not find information about potentiation of antiviral activity of modified nucleoside formulations when used with MPM or direct recommendations on the use of such combina-

[2]Content from elsevier's drug information. Drug Monograph Cidofovir – Elsevier. Available at: https://elsevier.health/en-US/preview/cidofovir

tions in clinical practice in the available literature. At the same time, the instructions for the use of MPM state that in such cases one should take into account the increase in plasma concentrations of ACV and MPA when using ACV or VACV simultaneously with MPM compared to those when using these drugs separately. This is probably due to the fact that they are competitors for excretion by tubule secretion[3].

Hydroxyurea (HU) has an insignificant effect on HSV-1 reproduction *in vitro*, causing depletion of intracellular pools of deoxyribonucleoside triphosphates (dNTPs) as a result of inhibition of cellular ribonucleotide reductase, which converts ribonucleotides into deoxyribonucleotides. This, in turn, favors the incorporation of nucleotide analogs competing with natural dNTPs (triphosphates of ACV, PCV, GCV, etc. and diphosphate of CDV) into viral DNA, which explains the subsynergistic or synergistic inhibitory effect of HU with these drugs on the replication of HSV-1 and HSV-2, respectively [43]. As noted above, cancer patients receiving chemotherapy have a high risk of reactivation of HSV infection. HU-based drugs Hydrea, Droxia, etc. are used in different types of cancer and are the standard treatment for sickle cell anemia. As follows from the instructions for use of Hydrea, taking antiviral drugs in case of HSV infection against the background of antitumor therapy with HU is not a contraindication. However, it is not recommended to use HU in patients with chickenpox, herpes zoster (pathogen – varicella zoster virus (VZV), or herpes type 3) and other acute infectious diseases[4].

Thus, traditional first-line antiviral drugs belonging to the group of modified nucleosides interact additively, while the use of second-line drugs is often accompanied by the development of severe side effects. Furthermore, if the virus develops drug resistance, it is not rational to include in the composition of combined etiotropic chemotherapy drugs whose efficacy has significantly decreased (to which resistance has developed). (Formulas of the compounds first mentioned in this subsection are given in **Table 4 of the Annex**).

Combinations including new anti-HSV drugs. New antiviral agents targeting biotargets other than HSV DNA-pol may serve as an alternative to nephrotoxic FOS and CDV in the treatment of first-line drug-resistant infections (ACV/VACV, FCV), and their combined use with first-line drugs (viral DNA-pol inhibitors) may simultaneously target different stages of the viral life cycle. These combinations may represent a preferred option for long-term suppression of viral load, including infections resistant to basic anti-herpetic drugs, and may also be useful for preventing the development of drug resistance in the virus. Research in this field is currently being actively pursued by research laboratories and leading pharmaceutical companies [44, 45].

A new class of antiviral drugs targets the helicase-primase complex (pUL5/pUL8/pUL52) of HSV, which unwinds the duplex DNA of the virus and initiates replication by synthesizing short RNA primers [23]. Amenalief (Maruho, Japan) based on amenamevir (AMV, ASP2151), an inhibitor of the helicase-primase complex of HSV and VZV, is the only drug that has been developed and introduced into clinical practice in recent decades for the treatment of shingles (VZV infection, 2017) and recurrent HSV (c 2023). Amenalief is licensed to date only in Japan[5]. Its efficacy as a therapeutic agent for the treatment of recurrent genital herpes is equivalent to that of VACV [46], even in immunocompromised patients, including cases of developed HSV drug resistance [47]. Due to severe side effects, an ongoing US randomized, double-blind, multicenter safety study of AMV in healthy volunteers (phase I, ClinicalTrials.gov identifier: NCT00870441) was discontinued. However, none of the described side effects (hepatotoxicity, renal impairment at higher doses, headache, thrombocytopenia, bleeding gums, erythema multiform, toxic epidermal necrolysis, Stevens–Johnson syndrome, and palpitations) have been identified as serious by the Japanese Risk Management Plan[5].

Pritelivir (PTV, BAY 57-1293, AIC316) is another HSV helicase/primase inhibitor, chemically unrelated to AMV, which is highly active exclusively against HSV without significant toxicity (AiCuris, Germany). The great advantage of PTV is that it can be administered once weekly due to its long half-life [48]. Unfortunately, a clinical trial of the safety and efficacy of PTV compared to VACV for prophylactic administration in healthy men and women with recurrent genital herpes HSV-2 (phase II) was suspended by the US Food and Drug Administration (FDA) in 2014 based on the results of a concurrent non-clinical toxicity study of PTV in monkeys. However, by time 56 participants out of 91 had completed the medication and according to preliminary results, PTV was superior to VACV in terms of efficacy and viral excretion reduction (ClinicalTrials.gov ID: NCT01658826) [49]. PTV is now in phase III clinical trials as a treatment for cutaneous mucosal HSV infection resistant or sensitive to ACV (Clinicaltrials.gov Identifier: NCT03073967) or with dual resistance to ACV and FOS (ClinicalTrials.gov Identifier: NCT05844436) in immunocompromised patients. PTV is not currently available as a marketed product.

Anti-herpetic combinations based on AMV and PTV are in preclinical development.

AMV paired and in triple combination with ACV and CDV acts *in vitro* additively to suppress HSV-1 infection [50], although an earlier publication noted a synergistic effect of combinations of AMV with ACV and PCV against ACV-sensitive strains of HSV-1, HSV-2 and VZV

[3]Mycophenolate mofetil. Vidal. Available at: https://www.vidal.ru/drugs/mycophenolate-mofetil-1

[4]Hydrea. Vidal. Available at: https://www.vidal.ru/drugs/hydrea__4396

[5]News Release. 2023.02.24. Maruho Receives Manufacturing and Marketing Approval for a Partial Change of the Indication and Dosage/Administration for Anti-herpes Virus Agent «Amenalief Tab. 200mg» for the Treatment of Recurrent Herpes Simplex in Japan. Available at: https://www.maruho.co.jp/english/information/20230224.html

in vitro, and in combination with Ara-A, a synergistic effect in the model of HSV-1 and VZV and an additive effect against HSV-2. In mice with HSV-1 zosterformis infection, combination therapy of AMV with VACV was more effective than monotherapy with these drugs [51].

The combined effect of ACV and PTV reduced the probability and rate of resistance to ACV and to both drugs simultaneously, while passaging of HSV in the presence of PTV in combination with FOS (15 passages) resulted in resistance only to FOS (sensitivity to PTV did not change). This suggests a high genetic barrier of combined therapy with PTV and FOS [52].

In a model of lethal herpetic encephalitis in mice infected with HSV-2, ACV and PCV interacted synergistically and effectively reduced animal mortality even when treatment was delayed by 72 h [53].

These results indicate that combination therapy of helicase-primase complex inhibitors with ACV and/or prodrugs of ACV and PCV could potentially be used to treat, for example, herpetic encephalitis or severe disseminated disease caused by HSV in immunosuppressed patients.

The oral medication Tembexa (Brincidofovir, BCV, CMX001, hexadecyloxypropyl CDV, CDV prodrug) was approved by the FDA in 2021 for the treatment of smallpox in adults and children, including neonates (Chimerix Inc., USA). BCV *in vitro* is also significantly superior to the efficacy of CDV and ACV against all human herpes viruses, including HSV-1 and HSV-2, including ACV-resistant strains [54]. It is significantly less nephrotoxic than CDV due to the fact that it is not a substrate for organic anion transporter proteins (hOAT1) and does not concentrate in the proximal renal tubules, its oral bioavailability is significantly superior to CDV (≤ 5%) and is 13.4% in tablet form and 16.8% in suspension form. Furthermore, BCV was found to penetrate the blood-brain barrier in mice[6]. The compound was well tolerated in phase I safety studies, and overall the potential of BCV for the treatment of CMV and HSV infections, including encephalitis, neonatal infections and ACV-resistant infections, seemed very high [55]. However, phase III efficacy studies of BCV for the prevention of CMV infection (ClinicalTrials.gov Identifiers: NCT02439957 and NCT02439970) were prematurely discontinued (2016): the former due to gastrointestinal toxicity [56] and the latter due to the results of the former (although again, patients experienced gastroenteritis, diarrhea, nausea and vomiting). Accordingly, the safety and dose-finding study of BCV for the treatment of neonatal HSV infection with central nervous system involvement (ClinicalTrials.gov Identifier: NCT01610765) was withdrawn due to the inability of this category of patients to access the study drug (2016). From then until now, there is no information about clinical trials on the safety and efficacy of BCV for the treatment of CMV and HSV infections. It is likely that for the same reason, although the *in vitro* combination of BCV and ACV synergistically suppresses replication of HSV-1 and HSV-2 and synergistically reduces mortality in mice infected with HSV-1 or HSV-2 [54], no further studies of this combination have been conducted. (Formulas of the compounds first mentioned in this subsection are given in **Table 5 of the Annex**).

[6]Tembexa. Highlights of prescribing information. Available at: https://www.chimerix.com/wp-content/uploads/2021/06/TEMBEXA-USPI-and-PPI-04June2021.pdf

Conclusion

Current etiotropic chemotherapy of infections caused by HSV is based on formulations of modified nucleosides and their prodrugs, which limits the possibilities of increasing the effectiveness of action on herpes during severe course of infection. Taking into account the increasing prevalence of HSV isolates resistant to this class of inhibitors in immunodeficient patients [19, 57], it is necessary not only to introduce into practice antiviral compounds with low toxicity, targeting viral proteins other than HSV DNA-pol and independent of TK, but also to develop combination therapy using drugs with alternative mechanisms of action.

The application of combinations of drugs acting on different targets, in case of synergistic interaction, allows reducing their doses while maintaining the effectiveness of treatment, which, in turn, minimizes toxic side effects associated with high doses of drugs when used individually, such as nephrotoxicity and neurotoxicity, or enhances the final therapeutic effect compared to each component separately. Intensive suppression of virus reproduction reduces the probability of induction of drug resistance, which is especially important in cases of immunosuppression and in the development of HSV infection in immunologically privileged organs, meaning primarily the eyes, brain and embryo. The introduction of AMV- and PTV-based drugs opens new possibilities for the development of highly effective drug combinations and has the potential to target HSV infections resistant to currently available anti-herpetic drugs. However, clinical trials are necessary to establish the real benefit of these new combinations for the treatment of HSV infections.

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Information about the authors:

Valeriya L. Andronova✉ – PhD (Biol.), Head of Laboratory, Leading Researcher at the Laboratory of Molecular Pathogenesis of Chronic Viral Infections, The N.F. Gamaleya Research Center of Epidemiology and Microbiology of the Ministry of Health of the Russian Federation, Moscow, Russia. E-mail: andronova.vl@yandex.ru; https://orcid.org/0000-0002-2467-0282

Georgy A. Galegov – D.Sci. (Biol.), Leading Researcher at the Laboratory of Molecular Pathogenesis of Chronic Viral Infections, The N.F. Gamaleya Research Center of Epidemiology and Microbiology of the Ministry of Health of the Russian Federation, Moscow, Russia.
E-mail: g.galegov@yandex.ru; https://orcid.org/0000-0001-6162-1650

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Информация об авторах:

Андронова Валерия Львовна✉ **–** канд. биол. наук, заведующая лабораторией, ведущий научный сотрудник лаборатории молекулярного патогенеза хронических вирусных инфекций ФГБУ «НИЦЭМ им. Н.Ф. Гамалеи» Минздрава России, Москва, Россия.
E-mail: andronova.vl@yandex.ru; https://orcid.org/0000-0002-2467-0282

Галегов Георгий Артемьевич – д-р биол. наук, профессор, ведущий научный сотрудник ФГБУ «НИЦЭМ им. Н.Ф. Гамалеи» Минздрава России, Москва, Россия. E-mail: g.galegov@yandex.ru; https://orcid.org/0000-0001-6162-1650

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