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Breaking the Resistance Barrier: A Mini-Review of the Advancements in Second-Line Treatments for HSV-1, HSV-2 and VZV Infections

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Abstract

This mini-review aims to evaluate a systematic review of the available literature on the efficacy of second-line treatments for Herpes Simplex Viruses (HSV) that are resistant to first-line antiviral agents. The systematic review included a search of six databases for eligible manuscripts using terms related to antiviral resistance, herpes, and HSV. A total of 137 articles were included in qualitative synthesis, examining the relationship between viral resistance to first-line treatments and potential second-line treatments in HSV. Of the included studies, 84.67% reported on HSV-1, with 34.31% of these studies reporting testing on resistant HSV strains. The following interventions were found to be effective as potential managements for resistant strains of HSV: nectin, amenamevir, methanol extract, monoclonal antibodies, arbidol, siRNA swarms, cucumis melo sulfated pectin, components from oleano europeae, griffithsin, morus alba L., nucleosides, botryosphaeran, monoterpenes, almond skin extracts, bortezomib, and flavonoid compounds. The available literature reviewed consistently supported the existence and potentiality of second-line treatments for HSV strains that are resistant to first-line treatments. Therefore, the review provided necessary information about treatment options for patients with resistant HSV infections, particularly those who are immunocompromised, and their providers.

Keywords: Infectious diseases; HSV; Drug resistance; Second-line treatment

Introduction

Herpes Simplex Virus (HSV) infections are of the most prevalent viral infections in humans, and antiviral agents, including acyclovir, ganciclovir, and foscarnet, are commonly used to manage these infections. However, drug-resistant HSV variants have been reported that are not effectively treated with these first-line treatments [1,2]. Immunocompromised patients are the primary population to present with viral strains that have mutations conferring resistance, and therefore, are at greatest risk [1,3]. While previous studies have evaluated the efficacy of second-line HSV interventions, there is a paucity of studies that have compared over 100 second-line interventions. Existing research has primarily focused on comparing efficacies and characteristics of primary medications for HSV, including acyclovir, ganciclovir, and foscarnet, as well as various plant extracts.

To evaluate the available literature on the possible efficacy of second-line treatments in HSV strains that are resistant to first-line treatments, a systematic review was performed of 597 pertinent studies on November 5, 2021 [4]. The search included all relevant literature using keywords including antiviral resistance, herpes virus, and HSV and were included if they reported the presence of an existing or potential second-line treatment for HSV-1, HSV-2, or Varicella Zoster Virus (VZV). Of the 597 studies, 137 articles met the inclusion criteria and were included in the final analysis. Elements such as type of study, sample characteristics, intervention descriptions, viral strain descriptions, mutations conferring resistance (if specified), and efficacy of interventions were extracted from each study.

Literature Review

HSV is one of the major causes of infections in humans that lead to severe symptoms, especially in immunocompromised patients such as neonates and transplant recipients [3]. It is essential to understand the viral replication cycle and the virus' cellular targets in order to properly treat HSV, particularly within immunocompromised populations. As a part of the Herpesviridae family, HSV is a double-stranded DNA enveloped virus that establishes life-long infections within its human host [5]. Although many drugs exist that target various portions of the HSV replication cycle, the emergence of antiviral-resistant strains within certain populations requires urgent reform in first-line viral treatments [3,5]. Antiviral drugs, in particular, play a vital role in the treatment and spread of HSV as they can be used both to inhibit an outbreak of the disease and to prevent infection [3]. Antivirals first arose with the creation of Iododeoxyuridine (IDU). IDU acts as a pyrimidine analogue and was the first effective antiviral drug that rose to fame as an anti-cancer drug in 1959 before researchers discovered that it could treat HSV keratitis [5]. Following this, other drugs such as trifluridine, an anti-tumor drug, and vidarabine rose in prominence but quickly fell due to their serious side effects and toxicity. As time went on, drugs arose that are still utilized today to treat viral infections like HSV such as antivirals, virucides, and immune response modifiers [5]. In the 1970s, the most common

first-line therapy used for HSV infections today was discovered: acyclovir. A synthetic guanine nucleoside analogue, acyclovir entered into clinical studies in 1977 when its development led Gertrude Elion to receive a Nobel Prize in 1988. Since then, there have been many additional anti-herpes viral treatments derived and approved for clinical use [5]. However, it is the consistent use of first-line second generation nucleoside analogue drugs, such as acyclovir, that have led to drug-resistant HSV variants [3]. The development of resistant variants has been associated with the prolonged use of antiviral drugs and/or suboptimal antiviral dose, although the presence of antiviral resistance has also been noted in the absence of a recognized history of antiviral treatment [5]. Nucleoside analogue resistances in HSV in immunocompetent individuals are not prevalent and have been reported at below 1%. However, in immunocompromised individuals infected with HSV, the rate of resistance ranges from 2.5%-30%, varying greatly depending on the severity of immunosuppression and underlying disease [5]. This leads to an especially difficult therapeutic challenge in treating immunocompromised patients [3]. This resistance has been thought to be attributed to alterations in the gene encoding viral Thymidine Kinase (TK) [5]. TK is not needed for viral replication, yet it plays an integral role in nucleoside analogue drug targeted therapies, thereby allowing mutant viruses to replicate and become resistant to the drugs' effects [5]. With the increasing prevalence of antiviral resistance in HSV and the limited efficacy of first-line drugs on resistant HSV strains, this mini-review highlights the urgent need to explore and review alternative second-line treatment options for managing HSV infections.

Discussion

The reviewed literature was shown to consistently support the existence and potentiality of second-line treatments for HSV strains that are resistant to first-line treatments [4]. The systematic review analysed a relatively large quantity of reports to a scope that has not yet been reported for second-line treatments in antiviral-resistant strains of HSV. From the systematic review, it was found that 93.43% of the reviewed papers reported that the proposed intervention was an effective potential management for resistant strains of HSV, while 2.19% of reviewed papers found the proposed intervention to be somewhat effective, and only 3.65% of reviewed papers found the proposed intervention to not be effective [4]. The interventions that were most commonly reported as effective potential managements for resistant strains of HSV included: nectin (in 2.19% of papers), amenamevir (2.19%), methanol extract (2.19%), monoclonal antibodies (1.46%), arbidol (1.46%), siRNA swarms (1.46%), cucumis melo sulfated pectin (1.46%), components from oleano europeae (1.46%), griffithsin (GRFT) (1.46%), morus alba L. (a compound from mulberry root bark extract) (1.46%), nucleosides (1.46%), botryosphaeran (1.46%), monoterpenes (1.46%), almond skin extracts (1.46%), bortezomib (1.46%), and various flavonoid compounds (1.46%) [4]. Additionally, while essential oils were found to be effective in 1.46% of papers, they were not effective in 0.73% of papers [4].

It should be noted here that a given study's efficacy was determined based upon each unique study design as well as statistical measures of importance, such as p values (accepted at $p<0.05$) [4]. Moreover, studies were evaluated for efficacy by their design and statistical power rather than various sample characteristics. Therefore, the systematic review contained a wide range of study designs and included samples ranging from Vero cells to guinea pigs. The majority of studies (88.32%) included *in vitro* elements, while the minority (16.79%) reported *in vivo* samples [4]. The broad spectrum of studies makes the systematic report stand out as it compares over 100 second-line interventions. Moreover, the abundance of studies with promising results highlights the need for human randomized controlled trials in this area. Developing novel therapies for antiviral-resistant strains of HSV is crucial, particularly in light of the growing health disparities affecting women's reproductive health due to shortages of OB-GYN professionals [6].

Finally, of the included studies, the majority (84.67%) tested their interventions on HSV-1, while 44.53% tested their interventions on HSV-2, and 5.11% tested their interventions on VZV. Over one third (34.31%) of all evaluated studies reported testing on resistant HSV strains. This aligns with the prevalence of HSV strains as HSV-1 is reported to affect over 70% of the world population, while HSV-2 is seen in 10% of the population [7]. However, all resistant strains of HSV included in the systematic review have been reported worldwide and have proven difficult to treat with standard therapies [5,7]. Additionally, infections with HSV are life long and have been reported to have a significant impact on a patient's life. This has become even more apparent as immunocompromised individuals; a population already at risk for severe infectious complications, are the patients most often reporting resistance [1,3]. This systematic review offers novel insights into the potentiality of second-line treatments for drug-resistant HSV strains and provides patients with valuable information about alternative treatment options [5].

Conclusion

Drug-resistant HSV variants are a growing concern in the management of HSV infections, particularly in immunecompromised patients. The manuscript "A Systematic Review of Second-line Treatments in Antiviral Resistant Strains of HSV-1, HSV-2, and VZV" suggests that second-line treatments for drug-resistant HSV strains exist and hold promise for future application. However, further studies are needed to determine the efficacy of these treatments in clinical settings. The systematic review provided supplementary information to patients on the potentiality of second-line treatments for HSV strains resistant to first-line treatments and is significant as it emphasized the importance of providing comprehensive research-supported clinical management for all patients, irrespective of their immune status. Because it offered essential information about treatment options for patients with drug-resistant HSV infections, it also assists healthcare providers in making informed decisions about managing these infections.

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Disclosures

All authors declare no conflict of interest.

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