Topical Imiquimod for Acyclovir-Unresponsive Herpes Simplex Virus 2 Infection

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A 34-year-old Hispanic man who had been diagnosed as having human immunodeficiency virus 5 years earlier presented with a 5-month history of herpes simplex virus (HSV) 2 infection of the penis. His CD4 cell count was 200/µL, and his viral load was undetectable. He had been receiving highly active antiretroviral therapy for 11 months. Before he developed HSV-2 infection, he had no history of genital herpes infection. Treatment was begun with acyclovir (400 mg 3 times daily for 1 month), with no improvement. Subsequently, the patient was treated with valacyclovir hydrochloride (1 g twice daily for 4 weeks) and then with famciclovir (500 mg 3 times daily for 4 weeks). Despite these multiple treatment attempts, he experienced no improvement and remained culture positive for HSV-2.

Topical imiquimod, an immunomodulatory drug, has been used and approved for the treatment of external genital and perianal warts. The case reported herein provides more compelling evidence for its broad applicability, particularly in treating acyclovir-unresponsive HSV-2 infections, based on its actions in altering immune function.

Since the late 1970s, the prevalence of HSV-2 infection has increased by 30%, and HSV-2 seropositivity is now detectable in roughly 1 of 5 persons 12 years and older nationwide. Because of the increased prevalence of HSV-2, there has been an increase in the use of acyclovir in its treatment. This increase in use is associated with the emergence of drug-resistant herpesvirus strains, commonly the result of a deficiency in the intracellular phosphorylation required for drug activation. Conventionally, foscarnet sodium has been the drug of choice in cases of acyclovir resistance. However, it too has been associated with drug-resistant strains owing to viral DNA polymerase mutants permitting replication despite drug presence.

Some success has also been seen with topical cidofovir in mice, as well as in humans, both healthy and immunocompromised. In 1997, an application to approve the use of topical cidofovir for acyclovir-resistant HSV was denied by the Food and Drug Administration, citing the need for phase 3 data. No further studies were planned. Adverse effects of cidofovir include nephrotoxic reactions associated with intravenous administration and an increased incidence of mammary tumors associated with subcutaneous administration in rats. Caffeine (Cafon) gel has been studied as well in a mouse model, with results suggesting its usefulness for acyclovir-resistant strains. Caffeine is known to inhibit replication of HSV-1, and the therapeutic efficacy of caffeine gel has been shown in a mouse model cutaneously infected with HSV-1.

Topical imiquimod offers yet another alternative for treatment of HSV infections, particularly in the setting of emerging resistance. The exact antiviral mechanism of imiquimod remains unknown. It has no direct antiviral effect in vitro studies. It is thought that its effects are di-
rectly related to its alteration of the immune response, targeting both the innate and cell-mediated pathways. Through the induction of cytokines, imiquimod can directly alter the innate immune response. It also alters cell-mediated pathways by the induction of interleukin 12 and alpha interferon, while inhibiting interleukins 4 and 5. Consequently, there is inhibition of the Th2 response and stimulation of the Th1 response, ultimately fostering a cytotoxic-specific immune response by the stimulation of lymphocytes to produce interferon gamma, a potent antiviral agent. In patients with human immunodeficiency virus whose immune system is sufficiently intact, imiquimod most likely exhibits antiviral activity through the same mechanism. The count threshold below which imiquimod would be ineffective is not clear at this time.

There have been many studies conducted with guinea pig models demonstrating the efficacy of topical imiquimod in the treatment of HSV infections. These studies suggest its role in the treatment of primary HSV infection, as well as its usefulness as adjuvant therapy with immunization using HSV glycoprotein and as suppressive therapy. In guinea pigs, it has been shown that the use of topical imiquimod is associated with a decrease in the number of primary HSV-2 lesions, a decrease in viral shedding, and a decrease in the viral content of the spinal cord. It has also been shown that immunization with HSV glycoprotein and imiquimod decreases the recurrence of HSV-2 infections compared with unimmunized controls. Furthermore, it has been shown that there is a decrease in recurrence even after topical imiquimod therapy is discontinued. These studies with guinea pigs, as well as the present case, provide compelling reasons to initiate clinical trials to confirm the efficacy of topical imiquimod therapy for HSV in humans.

Our case raises several points of interest. First, topical imiquimod, approved only for the use in genital and perianal warts, may also be an effective treatment for HSV infections, functioning as an immunomodulator rather than as a direct antiviral agent. Imiquimod up-regulates the antiviral immune response, instead of directly attacking the virus. Therefore, it offers an alternative strategy for combating HSV-2 infections, particularly in the setting of acyclovir resistance or unresponsiveness. First, because it is not a direct antiviral agent, it is unlikely to generate resistance itself. Second, as a topical treatment, it is easier to use, especially for patients already on the complex oral treatment regimens that are common in immunocompromised patients. This ease of use may increase patient compliance and decrease transmission. Third, management of recurrent HSV-2 disease commonly calls for daily doses of acyclovir for months to years, with recurrences likely after the discontinuation of therapy. Topical imiquimod therapy has been associated with a decrease in the number of recurrences in guinea pigs, even after treatment has stopped.

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REFERENCES


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