Valganciclovir and Human Herpesvirus–8

Clyde S. Crumpacker
Division of Infectious Diseases, Beth Israel Deaconess Medical Center, Boston, Massachusetts

(See the article by Casper et al., on pages 23–30.)

Ganciclovir is a nucleoside analogue of guanosine and is the mainstay of treatment against human cytomegalovirus (CMV), a γ-herpesvirus. Ganciclovir is phosphorylated by herpes simplex virus thymidine kinase or the protein phosphokinase (UL97) of cytomegalovirus to form ganciclovir monophosphate. Cellular kinases then form ganciclovir triphosphate, which is a potent inhibitor of viral DNA polymerase [1]. Ganciclovir triphosphate is an effective inhibitor of CMV replication, but it is not a chain terminator like acyclovir. In the presence of ganciclovir triphosphate, viral DNA replication is greatly slowed, but small fragments of CMV DNA around the origin of DNA replication continue to be made and ganciclovir monophosphate is incorporated into these small fragments of CMV DNA [2, 3].

In clinical use, human CMV can become resistant to ganciclovir and resistance mutations are found in 2 CMV genes, the UL97 protein phosphokinase and the CMV DNA polymerase. The ganciclovir resistance mutations in the UL97 gene cluster at amino acids 460 and 520, as well as from 590–607 [4]. A ganciclovir-resistant mutation results in a UL97 protein that is unable to phosphorylate ganciclovir. Only 6% of orally administered ganciclovir is bioavailable, which greatly restricts its oral use. By attaching a valine ester to ganciclovir (valganciclovir), the bioavailability of the orally administered drug is greatly increased to 68% [5]. A valine esterase in the human gastrointestinal mucosa cleaves the valine and results in ganciclovir in the portal blood circulation. A daily oral dose of 900 mg of valganciclovir twice per day is equivalent to an intravenously administered dose of ganciclovir of 5 mg/kg twice per day.

The article by Casper et al. in this issue of the Journal provides evidence that valganciclovir can also inhibit replication of human herpesvirus–8 (HHV–8), another γ herpesvirus [6]. Ganciclovir has been shown to be phosphorylated in the presence of both the HHV–8 thymidine kinase (open reading frame [ORF] 21) and the HHV–8 phosphotransferase (ORF36) [7]. Two other reports, however, provide conflicting evidence, which suggests that the thymidine kinase of HHV–8 does not phosphorylate ganciclovir [8, 9]. It is not completely clear, therefore, how ganciclovir is activated to ganciclovir triphosphate during HHV–8 infection. Phosphorylation by a cellular enzyme remains a possibility. It has also been shown that ganciclovir, cidofovir, and foscarnet inhibit the production of HHV-8 from latently infected cell lines upon stimulation, whereas acyclovir has little or no activity [10–12].

The possibility that ganciclovir or valganciclovir might inhibit HHV–8 replication and prevent development of Kaposi sarcoma in HIV-infected patients was suggested by the observation that patients who received 4.5 g daily of orally administered ganciclovir to prevent development of CMV retinitis in the eye without an ocular ganciclovir implant also had a lower incidence of Kaposi sarcoma in a large clinical trial [13]. This suggested the intriguing possibility that replicating HHV–8 expressed lytic proteins or stimulated cellular cytokines, which contributed to the development of Kaposi sarcoma. It has been suggested that in KS lesions, the lytic cycle gene products may be involved in proliferation of neighboring cells, contributing to pathogenesis by secretion of vascular endothelial growth factor, an angiogenesis activator. The expression of ORF74 induces an angiogenesis phenotype by secretion of vascular endothelial growth factor, an angiogenesis growth factor. The HHV–8 ORF74 can also activate mitogen-activated protein kinase, which indicates that the viral protein has a molecular specificity to trigger signaling cascades that are activated by inflammatory cytokines [15]. Another viral protein that may be a candidate for contributing...
to pathogenesis is the HHV-8 homologue of human IL-6, the vIL-6 protein. Thus, prevention of HHV-8 replication might provide therapeutic benefits in human disease.

This study by Casper et al. [6] provides evidence that valganciclovir is the first antiviral agent that has been shown to reduce HHV-8 replication in a randomized clinical trial. The study design was a double blind, placebo-controlled crossover trial in which 26 HHV-8 infected men were randomized to receive 8 weeks of valganciclovir or placebo (900 mg once per day administered orally). After a 2-week washout period, participants received the other study drug for 8 additional weeks. Oral swab samples were taken daily and analyzed for HHV-8 DNA and CMV DNA by real time PCR. Sixteen HIV-positive men and 10 HIV-negative men completed the study. Valganciclovir administered orally effectively inhibited mucosal HHV-8 replication, as detected by a sensitive PCR assay for HHV-8 DNA. The antiviral effect of valganciclovir reduced the frequency and quantity of HHV-8 that was detected in the oropharynx; this effect was prompt and occurred independently of the reduction in CMV replication. The Casper et al. [6] study also provided evidence that HHV-8 replication occurs independently of CMV replication in immunocompromised patients. The hematologic, renal, and hepatic toxicities of valganciclovir were similar to those of placebo in this short trial of low-dose valganciclovir.

The Casper et al. [6] study provides important new quantitative data that valganciclovir suppresses replication and oropharyngeal shedding of HHV-8 and sets the stage for additional research to determine whether valganciclovir prevents Kaposi sarcoma in patients at high risk due to immunosuppression. The effects of valganciclovir on other HHV-8 associated malignancies, such as primary effusion lymphoma and multicentric Castleman disease, should also be carefully evaluated.

References