CORRESPONDENCE

Effects of Famciclovir and Valacyclovir on Herpes Simplex Virus Type 1 Infection, Latency, and Reactivation in Mice: How Dissimilar Are Study Results?

To the Editor—LeBlanc et al. [1] assessed the effects of famciclovir and valacyclovir on herpes simplex virus (HSV) type 1 infection, latency, and reactivation in mice but did not demonstrate superiority of famciclovir over valacyclovir on the establishment of HSV latency in mice. Furthermore, they assert in both the Introduction and Discussion sections of their article that their results “differ notably from the serial comparative mouse studies of famciclovir and valacyclovir” [1, p. 598] published by my colleagues and me [2–5]. We wish to draw attention to 4 important points that we believe explain the declared discrepancy between studies in our 2 laboratories.

First, we infected a strain of moderate virulence (HSV-1 SC16) into the skin of the murine ear pinna, at a dose of 10^5 pfu per mouse. The experiments described by LeBlanc et al. [1] involved bilateral application of 10^6 pfu of the neurovirulent McKrae strain of virus to the scarified corneas. We believe that the latter method of inoculation would favor direct uptake of virus from the inoculum into the axons and rapid transfer to the ganglionic neurons. This then would lead to the establishment of unamplified latency within 24 h, as described by Simmons et al. [6]. A significant number of neurons would, therefore, contain latent HSV before the commencement of therapy on postinfection day 1. We would anticipate the effects of therapy under such conditions to be minimal. Furthermore, subtle differences between the 2 drugs may have been obscured.

Second, the experiments by LeBlanc et al. [1] resulted in 100% mortality, with deaths occurring on postinoculation days 4 and 5, suggesting that a severe neurologic infection was established very quickly in this model. Because there were no survivors in the untreated group, there were no positive control animals with which to compare therapy with either drug. By contrast, our experiments showed ~50% mortality without treatment (which usually occurred 6–10 days after infection). Mortality was reduced to 0 when treatment with either drug was started within 2 days after infection. Under these conditions, survivors were available for comparison with treatment groups [2–5].

Third, LeBlanc et al. state, “In contrast to prior studies that used the ear pinna model [2, 5], we did not observe a rebound of virus titers after cessation of valacyclovir therapy” [1, p. 596–7]. This statement appears to be at variance with the results reported by LeBlanc et al., since positive virus titers in trigeminal ganglia and brains are evident on day 11, the last day on which samples were tested for infectious virus. Therefore, the infection was not cleared by the end of the observation period, and, in any case, the animals were not tested daily, which in our experience is necessary for detection of transient recurrences of infectious virus. We question the statement that no “rebound” of infectious virus was seen, since samples were tested intermittently (days 2, 4, 7, 9, and 11 after infection) and before the acute infection was completely cleared. Indeed, some of our results would look similar to those published by LeBlanc et al. [1] if our data had been recorded only on alternate days.

Fourth, LeBlanc et al. state in their introductory text that Thackray et al. [2–5] claim that “famciclovir is better than valacyclovir in terminating ganglionic HSV infection and thereby limits subsequent reactivation” [1, p. 594]. We did not claim that either compound was superior in terminating ganglionic HSV infection; however, we reported a reduction in the amount of detectable latent virus measured by disaggregation, long-term culture of whole ganglia, in situ hybridization for latency-associated transcripts, and reduced rates of reactivation by explant culture [4]. In all cases, the reduction was greater for famciclovir, but neither compound resulted in the “termination” of latency.

For these reasons, we contend that the assertion by LeBlanc et al. that their data differ from ours should be judged cautiously. We see little justification for the proposal that the “McKrae-induced infection and disease closely resemble that seen in humans” [1, p. 598]. Indeed, this may not be a good model in which to compare the effects of nucleoside analogues on establishment of latency. We believe that further studies in a variety of laboratory-infection models are urgently required in order to fully interpret clinical data and to optimize treatment strategies using the 2 oral prodrugs, valacyclovir and famciclovir.

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References
Reply

To the Editor—Thackray and Field [1] raise 4 points that they believe explain why our recent study [2] failed to document the virologic superiority of famciclovir over valacyclovir that they described in several reports and numerous abstracts.

First, the route of infection did differ, as we acknowledged in our Discussion section [2]. They argue, however, that infection of the cornea (as opposed to the ear pinna in their model system) would favor direct uptake of virus into the axons, eliminating the opportunity a drug started 24 h later might have to limit viral amplification in the ganglia. We believe that any such aspect of our model system is overstated. In our studies, virus titers in tissues continued to rise for some days after the start of treatment (figure 3 in [2]). Thus, there remained ample opportunity for viral replication to be affected by the drugs. Nonetheless, we failed to observe any differential benefit of famciclovir. Moreover, Thackray and colleagues [3–5] reported experiments in which they delayed treatment even further and still observed superiority of famciclovir.

Second, Thackray and Field [1] are concerned about the virus inoculum that we used, because it was associated with universal mortality in the absence of treatment. It is true that no positive controls remained with which to compare the effects of treatment on latency and reactivation; however, untreated animals survived long enough for us to observe that famciclovir and valacyclovir were equivalent in virologic outcome measures of the acute infection.

Third, with regard to a rebound of virus titers, we disagree that there is a “variance with the results published” [1]. It has been our experience that the time points chosen are more than sufficient to track the spread of herpes simplex virus (HSV) from the eye to the trigeminal ganglia and into the brain. With the chosen time points, we saw the spread of virus through these tissues. Moreover, we detected no differences in the effect of either drug during the testing period. Obviously, for a true rebound to occur, the initial infection first must be cleared. Clearance was beginning to occur by the final time point, post-infection day 11. In an immunosuppression model, Field et al. [3] tested ear and brain samples on intermittent days and still detected a rebound of virus titers.

Fourth, we claimed equivalence of both drugs in “terminating ganglionic infection” [2], by which we meant the presence of infectious virus in the tissue. Despite their claim to the contrary, Thackray and Field [4, 5] reported that famciclovir was superior in reducing the amount of both infectious and latent virus in ganglia and in “preventing the establishment of latency” (Discussion in [4]; Introduction and Discussion in [5]).

We agree that each animal model has its own advantages and disadvantages. We believe, from our own data, that famciclovir and valacyclovir are equivalent for the acute treatment of HSV infections and will continue to believe so until a well-designed clinical trial proves otherwise.

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References


Questions about Results Reported with Potent Antiretroviral Therapy for Human Immunodeficiency Virus Type 1 Infection

To the Editor—Zaunders et al. [1] report the clearance rates of plasma human immunodeficiency virus (HIV) type 1 RNA and peripheral blood HIV-1 DNA levels, the phenotypic profiles of CD4 and CD8 lymphocytes, and anti–HIV-1 antibody levels in patients treated for 52 weeks with antiretroviral therapy (combination of zidovudine, lamivudine, and indinovir). Therapy was begun during primary HIV-1 infection (PHI). Results were compared with results for HIV-1–uninfected subjects, un-