Failure of Adjunctive Valacyclovir to Improve Outcomes in Herpes Simplex Encephalitis

Kenneth L. Tyler
Departments of Neurology, Medicine, and Immunology-Microbiology, University of Colorado School of Medicine, Aurora

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The majority of cases of acute encephalitis remain of unknown etiology despite extensive diagnostic evaluations [1, 2]. Herpes simplex virus (HSV) is the most common identified cause of acute sporadic encephalitis in the Western world, accounting for approximately 20% of total cases of identified cause [3]. Classic studies by the National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group (CASG) established intravenous acyclovir (ACV) as the standard of care for treatment of HSV encephalitis (HSE) [4]. Mortality in patients with brain biopsy–proven HSE dropped from 70% in placebo recipients [5] to 28% in those receiving intravenous ACV (30 mg/kg/day for 10 days) [4]. This impressive effect on mortality was also seen in a randomized multicenter trial in Sweden in which mortality was reduced to 19% in the ACV-treated group [6]. Despite this striking reduction in overall mortality, outcomes in survivors remain suboptimal. In the Swedish study, nearly one-third of ACV-treated survivors had moderate or severe sequelae [6], and in the CASG trial 42% of ACV-treated survivors had moderate or severe sequelae [4]. These results have been confirmed in subsequent studies that extended the duration of therapy to the now-standard 14–21 days and utilized cerebrospinal fluid (CSF) polymerase chain reaction (PCR) tests rather than brain biopsy to confirm the diagnosis of HSE [7]. In a multicenter study from France, mortality in ACV-treated patients was only 15%, although 57% of survivors continued to have moderate or severe disability at 6 months [7]. These studies indicate that there remains significant room for improvement in outcomes of patients with adult HSE. A recent multicenter, randomized, placebo-controlled trial in neonatal HSV central nervous system (CNS) disease has shown that adding oral ACV (300 mg/m² three times daily) for 6 months following a standard initial intravenous course of 14–21 days of ACV dramatically improves outcomes as measured by the Mental Development Index of the Bayley Scales of Infant Development [8]. Although neonatal HSV CNS disease differs from adult HSE in several significant ways, this study raised the possibility that supplemental treatment with an oral antiviral drug after initial intravenous ACV therapy might also improve outcomes in adult HSE. In this issue of Clinical Infectious Diseases, Gnann and colleagues present the results of just such a trial [9]. Following completion of a standard course of 14–21 days of intravenous ACV, patients with CSF PCR–proven HSE were randomized to an additional 90 days of oral valacyclovir (VACV) (2 g three times daily) or placebo. Unfortunately, the addition of oral VACV had no beneficial effect, and in some cases even had a negative effect (not significant) on cognitive function as assessed by either the Mini-Mental State Examination (MMSE) or the Mattis Dementia Rating Scale (MDRS) at 6, 12, or 24 months post-illness. Although the study result is plausible, the study has a number of significant limitations. Enrollment requirements excluded the most seriously ill patients, and, as noted by the authors, those enrolled were “a relatively high-functioning subset of HSE survivors.” It therefore remains unknown whether more seriously ill patients or those with associated immunocompromising conditions might still benefit from supplemental antiviral therapy.

Unfortunately, and despite the large number of study sites (N = 15) in North America and Europe, it took 8 years to enroll 91 patients (only 87 were actually randomized). Six US sites only enrolled an average of 1 patient every 3 years per site! This abysmal enrollment rate is not unique to this study. The pediatric trial described earlier [8] required >10 years to enroll 74 patients from 19 institutions.
These accrual rates reflect in part the rarity of the disease (HSE has an incidence of about 4 cases per million population per year), but also suggest that the entire model for designing and conducting antiviral trials for viral CNS infections needs to be reconsidered, as it simply is not an efficient mechanism for providing critically needed evidence-based data in a timely fashion for these often relatively rare disorders.

Negative results are always discouraging. Was anything useful learned from this study? As the authors note, this study did provide several intriguing insights into the outcome of HSE in the modern era. It was quite remarkable how well this selected population of subjects actually did. By 2 years post-illness, 91% of the subjects had no or mild impairment on the MMSE (a score of >23 out of 30), and 90% had no or mild impairment on the MDRS (a score of >121). The bulk of the improvement on these tests from baseline occurred (a score of >121). The role, if any, for adjunctive corticosteroids in HSE remains to be established. In a retrospective human study from Japan, the addition of corticosteroids to ACV significantly increased the odds ratio for a good outcome in patients with HSE by approximately 3.5-fold (95% confidence interval [CI], 99- to 12.09-fold) in single logistic regression analysis and by approximately 9-fold (95% CI, 1.13- to 70.99-fold) in multiple logistic regression analysis [11]. Unfortunately, a multicenter, randomized, double-blind, placebo-controlled trial of adjunctive steroids in Europe [12] failed to recruit an adequate number of subjects and was terminated. The recent observation that up to 30% of patients with HSE develop serum and/or CSF autoantibodies against the N-methyl-d-aspartate receptor [13] raises intriguing questions and potential therapeutic opportunities. If this autoimmune response contributes to disease pathogenesis or CNS tissue injury in a subset of patients (which remains to be established), then perhaps immunomodulatory therapies that are used to treat autoimmune encephalitides combined with antiviral therapy could have a role in the treatment of HSE. Interestingly, one of the first-line treatments commonly utilized for autoimmune encephalitis, intravenous immunoglobulin (IVIG), has been shown to protect mice from fatal HSE [14]. The actions of IVIG in this model are independent of HSV-specific antibodies and include suppression of CNS infiltration and subsequent degranulation by pathogenic CD11b+Ly6Chigh monocytes, expansion of regulatory T-cell populations, and increased accumulation of CD4+ interleukin 10–producing T cells in the CNS [14]. Finally, a growing body of studies suggests that human susceptibility to HSE is in some cases linked to deficiencies in Toll-like receptor 3 immune signaling pathways, including associated type 1 interferon responses [15]. This suggests that therapies designed to enhance these innate immune responses, such as treatment with interferon α/β might also be tested for therapeutic efficacy in HSE.

Perhaps the easiest target of all for improving survival and outcomes is simply to do better with therapy that we know works. Many studies have suggested that we need to dramatically improve performance in the use of empiric ACV therapy in patients with suspected encephalitis, and to address factors causing delays. In a retrospective study of ACV administration to patients with a high suspicion of acute encephalitis because of the presence of fever, CSF pleocytosis with a negative Gram stain, and altered mental status on admission to the emergency department, 71% of patients did not receive empiric ACV in the emergency department but only after inpatient admission and only after a median delay of 16 hours (95% CI, 7.5–44 hours) [16]. In a more recent study from Canada, ACV was not administered until a median of 21 hours after presentation in encephalitic cases and a median of 11 hours in the subset eventually found to have HSE [17]. Factors that can contribute to these delays include the associated presence of other severe underlying illnesses, a delay in brain imaging, and low CSF cell counts [18]. Surprisingly, in some settings, an important factor in delay is simply the failure to consider HSE in the differential diagnosis despite compatible and suggestive clinical and laboratory features [17].

Note

Potential conflict of interest. Author certifies no potential conflicts of interest.

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References