



**U**se of valganciclovir (Valcyte) in patients with elevated antibody titers against Human Herpesvirus-6 (HHV-6) and Epstein-Barr Virus (EBV) who were experiencing central nervous system dysfunction including long-standing fatigue.

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Montoya et al at Stanford University treated chronic fatigue syndrome patients with 6 months of valganciclovir (Valcyte) if they had elevated IgG tests for HHV-6 and EBV and had at least 4 of the following symptoms: impaired cognitive functioning, slowed processing speed, sleep disturbance, short-term memory deficit, fatigue and symptoms consistent with depression. Nine of the twelve treated patients (75%) “experienced near resolution of their symptoms, allowing them all to return to the workforce or full time activities.” In the nine patients with a symptomatic response to treatment, EBV VCA IgG and HHV-6 IgG titers significantly declined.

This is not a new finding, as previous studies as far back as 1997 have demonstrated significant improvement with similar antivirals (1,2,3). This study has, however, been much more publicized. We have been using Valcyte in our center for the treatment of chronic fatigue syndrome for over 4 years and have found it to be effective, especially in patients with the following: flu-like symptoms or having symptoms that started with a flu-like illness; elevated IgG or EA against Epstein bar virus, cytomegalovirus and/or HHV-6; low natural killer cell activity; high RNase-L activity; high ACE (>35); coagulation activation; high tumor necrosis factor (TNF); low melanocyte stimulation hormone (MSH); high interleukin-6 (IL-6); low WBC; increased 1-25 vitamin D/25 vitamin D ratio and/or elevated or decreased total IgA, IgM or IgG levels.

This study contributes more confirmatory evidence that IgM antibodies are not typically elevated in chronic reactivating infections so most patients are incorrectly told they do not have an active infection based on such testing. High IgG levels are diagnostic for an active infection in these patients, which is not what is taught in medical school and contrary to the belief of most physicians, including infectious disease specialists. This study also demonstrated the lack of sensitivity of standard PCR testing.

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# Use of valganciclovir in patients with elevated antibody titers against Human Herpesvirus-6 (HHV-6) and Epstein–Barr Virus (EBV) who were experiencing central nervous system dysfunction including long-standing fatigue

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## Abstract

**Background:** Twelve patients with long-standing symptoms of central nervous system (CNS) dysfunction were found to have elevated antibody titres to human herpesvirus-6 (HHV-6) and Epstein–Barr virus (EBV). All patients had four or more of the following neurocognitive symptoms: impaired cognitive functioning, slowed processing speed, sleep disturbance, short-term memory deficit, fatigue and symptoms consistent with depression.

**Objectives:** We sought to determine whether elevated antibodies to EBV and HHV-6 indicated chronic viral activation in patients with CNS dysfunction and if their symptoms could be improved by suppressing viral activity with oral valganciclovir.

**Study design:** Patients with high IgG antibody titers against HHV-6 and EBV who were suffering from central nervous system dysfunction and debilitating fatigue for more than one year (median 3 years, range 1–8 years) were treated with 6 months of valganciclovir in an open label study.

**Results:** Nine out of 12 (75%) patients experienced near resolution of their symptoms, allowing them all to return to the workforce or full time activities. In the nine patients with a symptomatic response to treatment, EBV VCA IgG titers dropped from 1:2560 to 1:640 ( $p=0.008$ ) and HHV-6 IgG titers dropped from a median value of 1:1280 to 1:320 ( $p=0.271$ ). Clinically significant hematological toxicity or serious adverse events were not observed among the 12 patients.

**Conclusion:** These preliminary clinical and laboratory observations merit additional studies to establish whether this clinical response is mediated by an antiviral effect of the drug, indirectly via immunomodulation or by placebo effect.

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## 1. Introduction

Chronic fatigue syndrome (CFS) is a clinically defined condition characterized by severe disabling fatigue and a constellation of symptoms that prominently feature self-reported impairment of concentration and short-term memory, sleep disturbances, and musculoskeletal pain. Patients suffering from CFS typically experience these symptoms for 6 months or longer. Suggested etiologies of CFS include, but are not limited to: viral or bacterial infections, endocrine-metabolic dysfunction, immunological imbalance, neurally mediated hypotension and depression (Afari and Buchwald, 2003; Fukuda et al., 1994). Most prior studies have found laboratory evidence that EBV and

HHV-6 are reactivated more often in patients with CFS than in healthy control subjects or disease comparison groups, but causal inferences have not been made from such an association.

Epstein–Barr virus (EBV) and human herpesvirus type 6 (HHV-6) are enveloped double-stranded DNA viruses belonging to the herpesviridae family. Both viruses are lymphotropic and neurotropic, and both are capable of producing latent infections with immunomodulatory effects (Ambinder, 2003; Ambinder and Lin, 2005; Krueger and Ablashi, 2003). Furthermore, in vitro studies of co-infection with both viruses have revealed that a significant interplay may occur between them (Cuomo et al., 1998; Flamand et al., 1993). The clinical consequence of this interaction remains unknown. However, it has been suggested by various investigators that infection with EBV and/or HHV-6

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