

therapy (Ussery *et al.*, 1988). However, one group has reported that intravitreal therapy alone failed to improve CMV retinitis (Orellana *et al.*, 1990).

Given the risk of disease in the contralateral eye, prudent clinicians should consider using oral VGCV to prevent disease in the unaffected eye while using intravitreal GCV. Current standard of practice in resource-poor areas where VGCV is not available involves treating active CMV retinitis with intravitreal GCV until the absolute CD4 count has risen to above 100 cells/ $\mu$ l for at least 3 months. In areas where VGCV is available, the current standard of practice for using intravitreal GCV is limited to a single dose administered at the time of CMV retinitis diagnosis only in those patients who have immediately sight-threatening retinitis (i.e. adjacent to the macula or optic nerve head), with therapy continuing with VGCV or with intravenous GCV in patients unable to take drugs by mouth. Although there are no randomized, controlled trials documenting the efficacy of intravitreal GCV in immunosuppressed patients other than those with late-stage HIV infection, case series and single-center studies support its efficacy (Langner-Wegscheider *et al.*, 2010; Agarwal *et al.* 2014). Because most cases of HIV-associated CMV retinitis now occur in resource-limited settings where neither GCV nor VGCV are available, the intravitreal route of administration has become the most common route of administration, globally, for this condition (Tun *et al.*, 2011). Although no longer being manufactured, efficacy of an implanted intravitreal GCV-eluting device was established in several small studies and then confirmed in two multicenter randomized trials (Musch *et al.*, 1997; Martin *et al.*, 1999).

### CMV GASTROINTESTINAL DISEASE

Treatment of AIDS-related CMV gastrointestinal disease with intravenous GCV may be associated with a more lasting response than is seen with CMV retinitis; esophagitis, gastritis, duodenitis, and adrenalitis, which are less common than retinitis as presentations of CMV disease in patients with late-stage HIV infection, respond favorably to intravenous GCV therapy and may be associated with prolonged periods of remission in the absence of maintenance therapy (Dietrich *et al.*, 1998; Wilcox and Schwartz, 1992; Fujii *et al.*, 1994; Zucker *et al.*, 1994; Sanhes *et al.*, 1995; Wilcox *et al.*, 1995). Oropharyngeal ulceration due to CMV responds well to GCV, and in one small series, patients did not require maintenance therapy (French *et al.*, 1991). While the response to therapy in patients with gastrointestinal CMV infection lasts longer than that in patients with retinitis, the proportion of patients who have a clinical response appears to be lower. In one retrospective analysis, GCV therapy resulted in resolution of pain and diarrhea in only 73% and 64% of the treated patients, respectively, whereas stabilization or improvement in retinitis occurred in ~ 82% (Jacobson *et al.*, 1988c). GCV has also been used effectively to treat CMV enterocolitis in young infants (Lim *et al.*, 1988).

Wasting associated with disseminated CMV infection has been reported to respond to GCV with improvement in body cell mass, weight, and energy (Kotler, 1991). In two reports, therapy with GCV did not correct liver function test abnor-

malities in patients with cholestasis possibly attributable to CMV infection (Jacobson *et al.*, 1988a; van der Ende *et al.*, 1992). Suspected CMV pancreatitis and subsequent relapses have been successfully treated with GCV (Calebunders *et al.*, 1994).

### CMV NEUROLOGIC DISEASE

A small proportion of patients with end-stage HIV infection develop central nervous system CMV disease, such as encephalitis, polyradiculitis, or myelitis.

Polyradiculopathy has been reported to improve after prolonged therapy with GCV, providing the CMV isolate is susceptible to the drug; however, the likelihood of success may be lower in advanced cases (de Gans *et al.*, 1990; Miller *et al.*, 1990; Cohen *et al.*, 1993; Kim and Hollander, 1993). In a study of 23 patients with lumbosacral polyradiculopathy, GCV therapy often caused worsening of symptoms for the first few weeks of therapy, but was generally associated with clinical stabilization (So and Olney, 1994). Combination foscarnet and ganciclovir therapy was reported to be of clinical benefit for this condition in two cases (Karmochkine *et al.*, 1994).

GCV is reported to have some beneficial effects in the treatment of CMV ventriculoencephalitis, although some patients developed cerebral disease while receiving intravenous GCV for other indications, and other patients died of cerebral disease despite intravenous GCV therapy (Schwarz *et al.*, 1990; Price *et al.*, 1992; Kalayjian *et al.*, 1993; Berman and Kim, 1994; Mastroianni *et al.*, 1994; Salazar *et al.*, 1995). Although viral replication in the central nervous system may be reduced by GCV, complete suppression does not appear to be possible, based on data from a few patients (Cinque *et al.*, 1995). However, combination therapy with both GCV and foscarnet was reported to result in a clinical response rate of 74% among 31 HIV patients with CMV encephalitis ( $n = 17$ ) or myelitis ( $n = 14$ ) (Anduze-Faris *et al.*, 2000). Combination therapy using GCV and foscarnet followed by alternating therapy with these agents as maintenance treatment also resulted in clinical improvement in a patient with CMV encephalitis that was resistant to GCV alone (Peters *et al.*, 1992). There is one report of successful treatment using GCV in an HIV-infected patient with meningoencephalitis due to VZV (Poscher, 1994).

### CMV PNEUMONITIS

CMV pneumonitis, an uncommon condition in patients with late-stage HIV infection, has been reported to respond to GCV (Eng *et al.*, 1992). Similarly, CMV infection of the larynx, an extremely rare condition in HIV-infected patients, has been reported to respond slowly to GCV therapy (Marelli *et al.*, 1992).

### PREEMPTIVE CMV TREATMENT OF CMV VIREMIC, HIV-INFECTED PATIENTS

A few studies have more recently evaluated preemptive treatment in HIV-infected patients (Wohl *et al.*, 2009; Mizushima *et al.*, 2013; Mattioni *et al.*, 2015). The largest of these was the prospective double-blind placebo-controlled trial conducted by Wohl *et al.* (2009). Patients with HIV, most of whom were