7. CLINICAL USES OF THE DRUG

Fomivirsen is indicated solely for the local intraocular treatment of CMV retinitis.

CMV retinitis is the most common ocular disease in HIV-infected patients with advanced immunodeficiency and it poses a significant visual threat to these patients (Kempen *et al.*, 2001; Kempen *et al.*, 2003; Avery *et al.,* 2014; Cunningham *et al.,* 2015; Huang *et al.,* 2015). Although reduced in incidence in HIV-infected persons with the advent of highly active combination antiretroviral therapy beginning in 1995–1996, CMV retinitis has by no means disappeared from that population (Jabs *et al.*, 2002; Adler *et al.,* 2014; Huang *et al.,* 2015). Further, patients immunosuppressed by drug treatment (for solid organ or stem cell transplantation) or other diseases (especially hematopoietic cancers) are also developing CMV retinitis (Cunningham *et al.,* 2015). A review of more than 1,100 patients who had organ transplants from 1995 to 2005 identified 33 patients with retinal complications, of whom 11 had CMV retinitis (Chung *et al.*, 2007). Xhaard *et al.* (2007) found 312 cases of CMV retinitis in over 14,000 patients who had received allogeneic hematopoietic stem cell transplantation from 1985 to 2001, with an incidence of 2.2%, whereas only one case of CMV retinitis was diagnosed among 1,306 transplantation patients in an earlier time period.

Optimally, patients with CMV retinitis should be treated initially with systemic therapy—ganciclovir–valganciclovir (see Chapter 215, Ganciclovir and valganciclovir), foscarnet (see Chapter 219, Foscarnet), or cidofovir (see Chapter 216, Cidofovir and brincidofovir), possibly in combination with local therapy (e.g. intravitreal ganciclovir) if warranted. However, systemic therapy may not be suitable because of preexisting conditions (e.g. severe neutropenia as a contraindication to ganciclovir therapy). Further, the patient may develop resistance or adverse reactions to these systemic agents during treatment (Jabs *et al.*, 1998a; Jabs *et al.*, 1998b), and resistance is associated with an increased risk of adverse ocular outcomes (Jabs *et al.*, 2003). An analysis of the susceptibility pattern of CMV isolates from blood or urine should be considered when evaluating the choice of therapy for ocular CMV infections.

For patients who have developed resistance or intolerance to systemic CMV therapy, fomivirsen may be an excellent alternative therapy (Vitravene Study Group, 2002c; Biron, 2006; Schreiber *et al.*, 2009). Fomivirsen therapy may also be useful as an adjunct to ongoing systemic therapy if the location or extent of retinitis warrants it. It may also be used if response to systemic therapy is slow.

7a. Cytomegalovirus retinitis in HIV-infected patients

As part of the development program for fomivirsen, several clinical trials were initiated in patients with HIV infection, all in the era before the widespread use of combination antiretroviral therapy. The first of these trials evaluated fomivirsen treatment in HIV-infected patients with advanced immunodeficiency and newly diagnosed CMV retinitis that was not immediately sight threatening (Vitravene Study Group, 2002a; Vitravene Study Group, 2002b). Patients were sequentially assigned, according to a computer-generated randomization list, to either immediate treatment with fomivirsen or to deferred treatment with close observation. The primary efficacy end point in this trial was the time to first progression of retinitis, assessed clinically and by review of standard fundus photographs evaluated in a masked fashion by experienced ophthalmologists in two independent reading centers. Treatment consisted of an intravitreal injection of fomivirsen 165 μg in 0.05 ml saline. For those patients assigned to the immediate treatment group, induction therapy consisted of three weekly doses of fomivirsen, followed by a single intravitreal injection given every other week (see Table 224.1). Treatment or observation was continued for 18 weeks or until clinical progression of CMV retinitis. Of the patients treated with fomivirsen (n = 18) the median time to first progression of CMV retinitis was 71 days compared with 13 days for patients (n = 10) in the deferred treatment group

Table 224.1 Summary of fomivirsen clinical trials.

Trial purpose	Evaluate drug efficacy/safety		Comparison of dosing regimens	
Patient population	Newly diagnosed or nonsight-threatening CMVR[a]		Reactivation of or persistent CMVR[b]	
Dose fomivirsen	165 μg/0.05 ml	Deferred treatment	330 μg/0.05 ml	330 μg/0.05 ml
Number of patients	18	10	37	21
Induction interval	Every week, three doses	No treatment; observation until progression	Every week, three doses	Two injections, 2 weeks apart
Maintenance interval	Every other week	No treatment; observation until progression	Every other week	Monthly
Median time to progression[d]	71 days	13 days p = 0.0001[c]	106 days	267 days p = 0.2179[c]

[a]Vitravene Study Group, 2002b.
[b]Vitravene Study Group 2002c (data from U.S./Brazilian study only; data from the second study not included because sample size was not met.
[c]Wilcoxon rank sum test.
[d]Estimated median time to CMVR progession by Kaplan-Meier analysis.
Abbreviation: CMVR: CMV infection of the retina.