

($p = 0.0001$, Wilcoxon rank-sum test) (Vitravene Study Group, 2002b).

Two further clinical trials were conducted to compare two different dosing regimens of fomivirsin in patients with CMV retinitis in whom the virus was reactivated or was persistently active even while they were being treated with systemic CMV antiviral drugs (Vitravene Study Group, 2002c). As in the previously mentioned study, efficacy assessment in these trials consisted of masked evaluations of fundus photographs. Because the patients in these studies had CMV retinal disease that was more advanced (i.e. persistently active), the dose of fomivirsin used (330 µg/0.05 ml) was double that used for newly diagnosed patients. These studies compared a more aggressive treatment schedule: an induction phase of three weekly injections followed by a maintenance schedule of injections every other week with an induction phase of two injections given 2 weeks apart followed by monthly injections as maintenance therapy (see Table 224.1).

The results from these studies evaluated a total of 106 eyes in 93 patients and demonstrated that there was no difference in treatment outcome between the two regimens. The median time to progression ranged from 106 days in one study to 403 days in the other (Vitravene Study Group, 2002c).

Fomivirsin is approved only for CMV retinitis associated with HIV infection, and it is almost always reserved as second-line therapy for this condition. Fomivirsin may also be considered (off-label use) to treat selected patients with CMV retinitis secondary to other causes of immunosuppression.

REFERENCES

- Adler H, De Gascun CF, McSweeney F (2014). Management of ganciclovir-resistant cytomegalovirus retinitis in HIV infection in the era of antiretroviral therapy. *Int J STD AIDS* **25**: 827.
- Aiello LP, Brucker AJ, Chang S et al. (2004). Evolving guidelines for intravitreal injections. *Retina* **24** (5 Suppl): S3.
- Anderson KP, Fox MC, Brown-Driver et al. (1996). Inhibition of human cytomegalovirus immediate-early gene expression by an antisense oligonucleotide complementary to immediate-early RNA. *Antimicrob Agents Chemother* **40**: 2004.
- Avery RL, Bakri SJ, Blumenkranz MS (2014). Intravitreal injection technique and monitoring: updated guidelines of an expert panel. *Retina* **34** (Suppl 12): S1.
- Azad RF, Brown-Driver V, Tanak AK et al. (1993). Antiviral activity of a phosphorothioate oligonucleotide complementary to RNA of the human cytomegalovirus major immediate-early region. *Antimicrob Agents Chemother* **37**: 1945.
- Biron KK (2006). Antiviral drugs for cytomegalovirus diseases. *Antiviral Res* **71**: 154.
- Chung H, Kim KH, Kim JG et al. (2007). Retinal complications in patients with solid organ or bone marrow transplantations. *Transplantation* **83**: 694.
- Cook PD (2001). Medicinal chemistry of antisense oligonucleotides. In Crooke ST, ed. *Antisense Drug Technology, Principles, Strategies and Applications*. New York: Marcel Dekker.
- Crooke ST (ed.) (2001). *Antisense Drug Technology, Principles, Strategies and Applications*. New York: Marcel Dekker.
- Crooke ST (2008). *Antisense Drug Technology, Principles, Strategies and Applications*. 2nd ed. Florida: CRC Press.
- Cunningham ET, Downes KM, Chee SP, Zierhut M (2015). Cytomegalovirus retinitis and uveitis. *Ocul Immunol Inflamm* **23**: 359.
- del Amo EM, Vellonen KS, Kidron H, Urtti A (2015). Intravitreal clearance and volume of distribution of compounds in rabbits: *in silico* prediction and pharmacokinetic simulations for drug development. *Eur J Pharm Biopharma* **95** (Pt B): 215.
- Grillone LR (2001). The development of antisense oligonucleotides as antivirals. In Crooke ST, ed. *Antisense Drug Technology, Principles, Strategies, and Applications*. New York: Marcel Dekker.
- Grillone LR, Lanz R (2001). Fomivirsin. *Drugs Today* **37**: 245.
- Henry SP, Miner RC, Drew WL et al. (2001). Antiviral activity and ocular kinetics of antisense oligonucleotides designed to inhibit CMV replication. *Invest Ophthalmol Vis Sci* **42**: 2646.
- Huang G, Jiang Q, Li, M et al. (2015). Retrospective study of cytomegalovirus retinitis complicated with acquired immunodeficiency syndrome. *Int J Clin Exp Med* **8**: 9537.
- Jabs DA, Enger C, Dunn JP, Forman M (1998a). Cytomegalovirus resistance and viral resistance: ganciclovir resistance. For the Cytomegalovirus Retinitis and Viral Resistance Study Group. *J Infect Dis* **177**: 770.
- Jabs DA, Enger C, Forman M, Dunn JP (1998b). Incidence of foscarnet resistance for cytomegalovirus retinitis. For the Cytomegalovirus Retinitis and Viral Resistance Study Group *Antimicrob Agents Chemother* **42**: 2240.
- Jabs DA, Martin BK, Forman MS et al. (2003). Cytomegalovirus resistance to ganciclovir and clinical outcomes of patients with cytomegalovirus retinitis. *Am J Ophthalmol* **135**: 26.
- Jabs DA, Van Natta ML, Kempen JH et al. (2002). Characteristics of patients with cytomegalovirus retinitis in the era of highly active antiretroviral therapy. *Am J Ophthalmol* **133**: 48.
- Jager RD, Aiello LP, Patel SC, Cunningham ET (2004). Risks of intravitreal injection: a comprehensive review. *Retina* **24**: 676.
- Kempen JH, Jabs DA, Dunn JP et al. (2001). Retinal detachment risk in cytomegalovirus retinitis related to the acquired immunodeficiency syndrome. *Arch Ophthalmol* **119**: 33.
- Kempen JH, Jabs DA, Wilson LA et al. (2003). Risk of vision loss in patients with cytomegalovirus retinitis and acquired immunodeficiency syndrome. *Arch Ophthalmol* **121**: 466.
- Leeds JM, Henry SP, Bistner S et al. (1998). Pharmacokinetics of an antisense oligonucleotide injected intravitreally in monkeys. *Drug Metab Dispos* **26**: 670.
- Leeds JM, Henry SP, Truong L et al. (1997). Pharmacokinetics of a potential human cytomegalovirus therapeutic, a phosphorothioate oligonucleotide, after intravitreal injection in the rabbit. *Drug Metab Dispos* **25**: 921.
- Mulamba GB, Hu A, Azad RF et al. (1998). Human cytomegalovirus mutant with sequence-dependent resistance to the phosphorothioate oligonucleotide fomivirsin (ISIS 2922). *Antimicrob Agents Chemother* **42**: 971.
- Schreiber A, Harter G, Schubert A et al. (2009). Antiviral treatment of cytomegalovirus infection and resistant strains. *Expert Opin Pharmacother* **10**: 191.
- Vitravene Study Group (2002b). A randomized, controlled clinical trial of intravitreal fomivirsin for treatment of newly diagnosed peripheral cytomegalovirus retinitis in patients with AIDS. *Am J Ophthalmol* **133**: 467.
- Vitravene Study Group (2002c). Randomized, dose-comparison studies of intravitreal fomivirsin for treatment of cytomegalovirus retinitis that has reactivated or is persistently active despite other therapies in patients with AIDS. *Am J Ophthalmol* **133**: 475.
- Vitravene Study Group (2002a). Safety of intravitreal fomivirsin for treatment of cytomegalovirus retinitis in patients with AIDS. *Am J Ophthalmol* **133**: 484.
- Vollmer J, Janosch A, Laucht M et al. (2002). Highly immunostimulatory CpG-free oligodeoxynucleotides for activation of human leukocytes. *Antisense Nucleic Acid Drug Develop* **12**: 165.
- Xhaard A, Robin M, Scieux C et al. (2007). Increased incidence of cytomegalovirus retinitis after allogeneic hematopoietic stem cell transplantation. *Transplantation* **83**: 80.