Management of Cytomegalovirus Retinitis in HIV and Non-HIV Patients

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In the modern era of highly active antiretroviral therapy (HAART) for human immunodeficiency virus, opportunistic infections including cytomegalovirus retinitis (CMVR) are seen with decreasing frequency. In the AIDS epidemic of the late-twentieth century, CMVR was a disease that affected transplant recipients requiring chronic immunosuppression.1 Early in the AIDS era, CMVR was the leading cause of intraocular infection, whereas the advent of HAART stemmed its incidence by 80% to 90%.2 Currently, ophthalmologists encounter CMVR in outpatient and hospital settings as a complication of compromised cellular immunity relating to HIV infection, systemic immunosuppression after transplantation, or chemotherapy for systemic malignancy. For this reason, recognition of the multiple options for the management of CMVR, including antiviral drug resistance, is paramount for effective care.

CLINICAL EVALUATION AND OCULAR FLUID ANALYSIS

CMVR typically presents as one of three classic morphologies: fulminant hemorrhagic retinitis, indolent granular retinitis, or frosted branch angiitis. These pathognomonic appearances, in addition to ocular fluid analysis, which has a greater than 80% sensitivity for detecting CMV DNA when present, allow ophthal-
Practical Retina

While monitoring CMVR patients receiving therapy, Smith and colleagues showed that of 21 eyes with clinically active retinitis, 20 (95%) had positive qualitative PCR, whereas no eye with clinically quiescent retinitis (n = 16) had positive PCR. Statistically significant positive linear correlations were found between quantitative DNA PCR and areas of active retinitis. In cases of recurrent or refractory retinitis, ocular fluid analysis by PCR for the presence of ganciclovir resistance mutations (UL97 and UL54) can help guide antiviral choice in these difficult scenar-
The development of valganciclovir, an oral prodrug of ganciclovir, has contributed to significant advancement in the treatment of CMVR. Due to increased oral bioavailability over ganciclovir, it has become the mainstay of treatment of CMV retinitis in the AIDS patient for induction and maintenance therapy. In 2002, the Valganciclovir Study Group demonstrated equivalently low rates of CMV progression, similar to previous trials, in patients randomly assigned to either oral valganciclovir (900 mg twice daily) or intravenous ganciclovir (5 mg/kg twice daily), 10% versus 9.9% after 4 weeks of induction therapy.13

With the increasing utilization of intravitreal drug delivery in the management of vitreoretinal disease, one important and timely question is related to the role of intravitreal antiviral therapy either as monotherapy or in combination with systemic antiviral for CMV retinitis. Jabs et al. reported results from 250 patients treated for AIDS related CMVR with systemic versus intravitreal therapy. These results demonstrated a 50% reduction in mortality, a 90% reduction in new visceral disease, and an 80% reduction in fellow eye involvement when treating with a systemic agent.

When compared to systemic regimens, intravitreal therapy alone demonstrated three-times-greater risk of retinitis progression (hazard ratio [HR] = 3.4) and five-times-greater risk of visual field loss (HR = 5.5).14 Although progression to foveal involvement is a concern in patients with zone 1 disease not involving the fovea, the benefit of intravitreal antiviral therapy is not clear. Because of the benefit to mortality and systemic morbidity, the use of systemic antiviral is important, however, with infectious disease consultation given the side effects of antiviral medications that require monitoring.

We will consider intravitreal antiviral therapy if there is zone 1 disease that is threatening the fovea, and each case is considered individually depending on the systemic health of the patient, ability of the patient to follow-up, and status of the fellow eye. For patients with recurrent disease or concerns for drug resistance, intravitreal antiviral therapy may still overcome “relative” drug resistance and should be considered, particularly in patients in whom CMV retinitis recurrence is observed after long-term prophylactic antiviral.

Non-HIV–Related CMVR

Non-HIV–related CMVR has recently been termed chronic retinal necrosis due the more indolent, granular retinitis and occlusive vasculopathy that can be present.15 Given the underlying myelotoxic-
ity that frequently accompanies immunosuppressed transplant recipients and cancer patients, systemic therapy is not always feasible or must be delivered at reduced dosing. As mentioned previously, systemic ganciclovir can worsen pre-existing myelosuppression and foscarnet is not available in an oral derivative. Therefore, in the non-HIV patient, intravitreal therapy allows for retinitis regression while reducing systemic medication side effects. Agarwal et al. recently reviewed a retrospective cohort of non-HIV CMVR patients who were treated with intravitreal ganciclovir (2mg/0.1mL) alone at least once weekly. Thirteen eyes received a total of 5.54 ± 3.36 injections with an average interval of 10 days during a period of approximately 6 weeks during the study. Each eye demonstrated clinical quiescence during the period, and no eye demonstrated recurrence while on therapy. Other series have purported success with intravitreal ganciclovir and foscarnet in conjunction with systemic therapy as tolerated. Because of the systemic toxicities related to ganciclovir (ie, myelosuppressive, renal) and foscarnet (ie, nephrotoxicity, electrolyte disturbances), the treatment of CMVR in the non-HIV patient may require intravitreal antiviral delivery augmented with systemic therapy as tolerated and prescribed in conjunction with the hematologist/oncologist and infectious disease specialist.

Retinal Detachment

Retinal necrosis, atrophy, inflammation, and scar formation predispose the retina affected by CMVR to complicated retinal detachment. Retinal detachment can occur early in the disease as demonstrated by Yen et al., who reviewed 64 cases of CMVR related retinal detachment and determined the median time to detachment from diagnosis was 1.5 months. Retinal detachment surgery in CMVR is typically performed with pars plana vitrectomy and silicone oil tamponade. Irvine et al. reported a consecutive series of 83 eyes that underwent vitrectomy with oil for CMVR related retinal detachment. Despite 81% of eyes having a macular detachment at time of surgery, 32% achieved 20/50 or better vision and two-thirds achieved at least 20/100 vision postoperatively. Two more recent reviews of retinal reattachment surgery with vitrectomy in Asian and Indian populations in the post-HAART era demonstrate excellent rates of anatomic success and similar visual outcomes, suggesting that antiretroviral therapy is independent of success of surgical outcomes.

SUMMARY

As CMVR continues to affect HIV-positive and non-HIV immunosuppressed patients, ophthalmologists must continue to tailor diagnostics and therapeutics to individual cases. In HIV-related disease, ocular fluid sampling and intravitreal drug delivery are considerations, but systemic antiviral therapy is paramount in the initial management from both ophthalmic and systemic morbidity endpoints.

Non-HIV–related disease should be approached with a multidisciplinary team, including an ophthalmologist/vitreoretinal/uveitis specialist for consideration of intravitreal antiviral therapy with qualitative and quantitative aqueous PCR monitoring, and consideration of PCR genome sequencing for CMV strains that may become resistant to antiviral therapies from long-term antiviral prophylactic exposure. Hematologists or oncologists may help with patients who remain bone marrow-suppressed following transplantation or systemic chemotherapy. Because of related toxicities of the anti-CMV medications and immunosuppressive medications (eg, bone marrow suppression and cytopenias), infectious disease consultation can help in the treatment and monitoring of side effects.

REFERENCES


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