Review

Changing patterns of HIV related ocular disease

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Cytomegalovirus (CMV) retinitis is the commonest ocular complication of AIDS and the prevention of recurrence has been dependent on lifelong maintenance treatment. Recently there has been a dramatic downturn in the number of new cases of CMV retinitis, which has been attributed to the introduction of highly active antiretroviral therapy (HAART) and subsequent improved survival. Whereas paucity of inflammation has been considered to be the hallmark of the ophthalmic manifestations of AIDS, with immune recovery, a new pattern of ophthalmic AIDS has emerged. This is characterised by a heightened inflammatory response and more frequent complications associated with this response—for example, vitritis, cystoid macular oedema. In spite of this, regression of CMV retinitis has been reported, as well as absence of reactivation or progression after withdrawal of anti-CMV maintenance treatment. How long this situation will continue is not known and we remain cautious about the future of CMV retinitis and other opportunistic ocular infections.

(*Sex Transm Inf* 1999;75:18–20)

Keywords: HIV; ocular disease; cytomegalovirus

Cytomegalovirus (CMV) retinitis is the commonest ocular complication of the acquired immunodeficiency syndrome (AIDS), affecting up to 45% of patients with CD4+ T lymphocyte counts of less than $100 \times 10^6/l$.^{1–6} Visual loss, including blindness, is the major complication with treatment involving the use of ganciclovir, foscarnet and, more recently, cidofovir. Therapeutic strategies have included administration by a variety of routes; intravenous, oral, intravitreal injection, or intravitreal device depending on which drug was used.^{7–11} All are effective in controlling retinitis, but are virostatic and therefore do not eradicate retinal CMV in severely immunosuppressed individuals.^{12–13} Prevention of recurrent CMV retinitis has been dependent on lifelong maintenance treatment. Despite the availability of effective treatment to control the retinitis a number of important problems have arisen. Drug related adverse reactions were common and included neutropenia (ganciclovir), nephrotoxicity (foscarnet, cidofovir), intraocular inflammation, and hypotony (cidofovir).^{2–14–15} Prolonged use resulted in the emergence of drug resistant strains^{16–18} and relapses invariably occurred. The time between relapses became progressively shorter and the reactivated retinitis appeared increasingly more

aggressive and more difficult to treat.^{2–19} Treatment of frequent recurrences required switching from one agent to another or using combination therapy. Although new anti-CMV drugs were being developed ophthalmologists were becoming increasingly pessimistic with regard to preserving vision in their patients.

Over the past 2 years there has been a dramatic downturn in the number of new cases of CMV retinitis. The introduction of highly active antiretroviral therapy (HAART) has been instrumental in modifying the clinical course of CMV retinitis. Epidemiological studies have shown that since the introduction of protease inhibitors in 1995, there has been a decrease in the incidence of AIDS defining diagnoses, opportunistic infections, including CMV retinitis, and mortality among patients infected with HIV.²⁰ In 1994, the cumulative incidence of *Pneumocystis carinii* pneumonia, *Mycobacterium avium* complex disease, and CMV retinitis was 21.9 per 100 person years and by the second quarter of 1997 it had reduced to 3.7 per 100 person years. This reduction was in part due to prophylaxis against *Pneumocystis carinii* and *Mycobacterium avium intracellulare*, but was largely credited to the use of HAART. A recent study confirmed a significant increase in survival of AIDS patients with CMV retinitis who were treated with HAART.²¹ HAART is effective in suppressing the viral load and reconstituting CD4+ T lymphocytes^{22–25} with a resultant increase in the time interval between relapses of CMV retinitis. Evidence is mounting that as sufficient immune reactivity against opportunistic infections, such as CMV, is restored, discontinuation of anti-CMV maintenance therapy should now be considered.^{26–28} In a series of eight patients (12 eyes) where anti-CMV therapy was discontinued, no reactivation or progression of retinitis was seen during the mean follow up period of 11.4 months and retinitis did not develop in previously unaffected contralateral eyes.²⁷ The toxic effects of maintenance and drug resistance were therefore avoided, but at the risk of possible visual loss should reactivation of the retinitis occur, particularly in patients with healed peripapillary or juxtafoveal lesions. Nevertheless, many patients now have their anti-CMV maintenance therapy withdrawn.

The replenished CD4+ T lymphocyte count induced by HAART is partly responsible for the emergence of a new pattern of ophthalmic AIDS, which is characterised by a heightened inflammatory response and more frequent complications associated with this response.^{29–30} In some patients with inactive CMV retinitis, the T lymphocyte rejuvenation is thought to

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Accepted for publication 5 January 1999

mount an immune response to ocular CMV proteins which is seen as a vitreous inflammatory reaction occasionally associated with papillitis or cystoid macular oedema (CMO).³¹⁻³² This response has been termed immune recovery vitritis and usually occurs shortly after the initiation of protease inhibitors.³¹⁻³⁴ Yet, many patients on combination antiretroviral therapy with partial immune reconstitution and inactive CMV retinitis do not develop inflammatory signs. Factors giving rise to the inflammatory response are unclear, but there have been indications that these CD4+ T lymphocytes are only partially functional and give limited protection.³⁵⁻³⁶ Consequently, there is conflicting evidence on the effects of HAART on CMV retinitis. Many authors report regression of CMV retinitis³¹⁻³⁷⁻³⁸ while others have found that it occurs in previously unaffected eyes, though this tends to happen in the first few weeks when the CD4+ T lymphocyte restoration is not complete.³³ Despite HAART, the CD4+ count in some patients will remain low and recurrences will occur.³⁴ Although the decline in the incidence of CMV retinitis has been attributed to improved immune function, in some cases this decline predated the commercial availability of protease inhibitors.³⁹

Whereas paucity of inflammation has been considered to be the hallmark of the ophthalmic manifestations of AIDS such as CMV retinitis, *Pneumocystis carinii* choroiditis, progressive outer retinal necrosis, and herpes simplex keratitis profound inflammatory reactions have been seen in ocular toxoplasmosis, fungal endophthalmitis, acute retinal necrosis, bacterial keratitis, and syphilis. Inflammatory reactions have also been reported as adverse reactions to drugs such as rifabutin⁴⁰ and cidofovir.¹⁵ With immune recovery, HIV itself has been thought to cause intraocular inflammation in the absence of other pathogens.⁴¹⁻⁴³ Patients with anterior uveitis refractory to topical and systemic corticosteroids, with HIV culture positive aqueous samples, have been found to respond to oral zidovudine.⁴² Zidovudine has also been observed to affect the clinical appearance of multifocal retinal infiltrates, which have been found to be located diffusely or in clusters, in the peripheral fundus.⁴³ These two findings, along with a mild to moderate vitritis, have been seen to coexist and are thought to represent features of a new spectrum of HIV disease in the eye.⁴³

Cystoid macular oedema (CMO) causing loss of central vision, previously an infrequent occurrence with active CMV retinitis,⁴⁴⁻⁴⁷ is now an increasing cause of visual loss in patients with AIDS and inactive CMV retinitis (fig 1).³¹⁻⁴⁸ The aetiology is poorly understood, but it is thought that as the immune function improves, choroidal inflammation may be a causal factor. Whereas CMO associated with active CMV retinitis may respond to systemic antivirals, CMO associated with inactive CMV is more problematic. Effective treatment is essential, particularly as patients may already have extensive peripheral (navigational) visual loss from previous (now inactive) CMV retini-

Figure 1 Fundus fluorescein angiogram of the left eye of a patient with extensive, inactive cytomegalovirus retinitis. There is diffuse leakage of dye (white) with cystoid macular oedema (arrowed).

tis and are now at threat of losing their central (reading and writing) vision. Oral acetazolamide and topical non-steroidal agents have limited efficacy and despite the possible risk of CMV reactivation, treatment strategies include corticosteroids given as periocular injections or by mouth.

Since first described as a discrete entity in 1981⁴⁹ the clinical and ophthalmic manifestations of AIDS have been found to be constantly evolving. Milestones in this evolution have been the introduction of reverse transcriptase inhibitors, prophylaxis against opportunistic infections, and the use of protease inhibitors. Each has contributed to decreasing the severity of the clinical features and increasing life span.⁴⁹⁻⁵³ HAART induced immune enhancement has been crucial in reducing morbidity and mortality. It has set the stage for a debate on whether prophylactic treatment for opportunistic infections is essential, but at the expense of developing paradoxical exuberant inflammation and its associated complications.³⁸ Nevertheless, it is evident that HAART associated improved immune function is changing the fundamental clinical features currently associated with AIDS. How long this situation will continue is not known and the anxiety is that we may be facing the prospect of CMV retinitis and other opportunistic ocular infections becoming widespread again.

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