Ocular complications of intravenous cidofovir for cytomegalovirus retinitis in patients with AIDS

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CLINICAL STUDY

Abstract

Purpose **To describe the frequency of anterior uveitis and ocular hypotony in cidofovir-treated patients with acquired immune deficiency syndrome (AIDS)-related cytomegalovirus (CMV) retinitis.**
Methods **A retrospective review was performed of all patients with AIDS-related CMV retinitis during a 12-month period. The CMV retinitis activity, concurrent illnesses and medications, and CD4$^+$ lymphocyte count were recorded in addition to the degree of anterior chamber inflammation and intraocular pressure at each visit. The frequency of uveitis and ocular hypotony in cidofovir-treated patients was determined and the possible influence of other ocular and systemic factors considered.**
Results **Eight of 9 patients on cidofovir developed anterior uveitis. The cellular anterior chamber activity resolved with topical corticosteroid administration in all eyes with uveitis but significant flare persisted despite topical steroids in 3 patients. Posterior synechiae responded poorly to topical mydriatic therapy, resulting in inadequate mydriasis which significantly limited the fundal view. One patient developed a visually significant unilateral hypotonous maculopathy.**
Conclusions **Patients treated with intravenous cidofovir for AIDS-related CMV retinitis are at significant risk of ocular adverse effects. Prompt treatment with topical corticosteroids and mydriatics may control uveitis and in some cases cidofovir treatment may be cautiously continued. In the event of ocular hypotony cidofovir should be discontinued in favour of an alternative anti-cytomegaloviral agent.**

Key words Cytomegalovirus retinitis, Uveitis, Hypotony, Cidofovir

Cytomegalovirus (CMV) retinitis is the commonest intraocular opportunistic infection in patients with the acquired immune deficiency syndrome (AIDS).[1] Although the introduction of highly active anti-retroviral therapy (HAART) has been associated with a reduced incidence of CMV retinitis,[2] improved survival has led to an increasing prevalence[3] and CMV infection remains a major cause of visual loss in patients with AIDS. Treatment of CMV retinitis with daily intravenous ganciclovir or foscarnet necessitates a permanent indwelling intravenous catheter, is time-consuming and is associated with relatively high rates of CMV reactivation[4] and adverse effects, including bone marrow suppression[5] and renal toxicity.[6] Local treatment by serial intravitreal injections or sustained-release intravitreous implants is effective but may be difficult to tolerate,[7] causes local adverse effects including retinal detachment,[8] and fails to protect against contralateral ocular and systemic CMV disease.

Cidofovir dihydrate (1-(1,3-dihydroxy-2-phosphonomethoxypropyl)cytosine dihydrate, or HPMPC) is a relatively new nucleoside analogue that effectively delays progression of CMV retinitis[9] in patients with AIDS. Following intracellular phosphorylation to its active metabolite, cidofovir selectively inhibits viral DNA synthesis by competitive inhibition of viral DNA polymerase. Intravitreal injection of cidofovir at 5- to 6-week intervals is highly effective[10] but has been associated with uveitis in up to 71% of patients[10–14] and ocular hypotony which may be visually significant and irreversible.[10,11] Intravenous infusions of cidofovir 5 mg/kg, once weekly for 2 weeks then once every other week, effectively slow the progression of CMV retinitis. Infrequent administration is possible as a result of cidofovir's prolonged duration of effect and an indwelling intravenous catheter is not normally required. Recent reports suggest, however, that uveitis and ocular hypotony occur even after intravenous cidofovir therapy.[15,16] In this study our aim was to describe the frequency of

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anterior uveitis and ocular hypotony in cidofovir-treated patients with AIDS-related CMV retinitis in two London ophthalmology departments.

Methods

A retrospective review was performed of all patients with AIDS-related CMV retinitis attending two ophthalmology departments during the 12-month period September 1996 to August 1997. In each case the CMV retinitis activity, concurrent illnesses and medications, and $CD4^+$ lymphocyte count were recorded in addition to the degree of anterior chamber inflammation (cells, flare, keratic precipitates and posterior synechiae) and intraocular pressure at each visit during the study period.

Treatment with intravenous cidofovir was given according to a standardised protocol including pretreatment and concomitant oral probenecid and intravenous hydration. Ocular hypotony was defined as an intraocular pressure of 5 mmHg or less. The frequency of uveitis and ocular hypotony in cidofovir-treated patients was determined and the possible influence of other ocular and systemic factors considered. Statistical analysis was performed using a chi-squared test with Yates' correction for small numbers.

Results

A total of 26 patients (25 men and 1 woman; mean age 38.4 years, range 31–58 years) with CMV retinitis attended during the study period. Nine patients received intravenous cidofovir. Eight (89%) of the 9 patients who received intravenous cidofovir subsequently developed anterior uveitis.

The numbers of patients with potential risk factors for anterior uveitis are shown in Table 1. Anterior uveitis was significantly associated with concurrent use of intravenous cidofovir but not with concurrent use of rifabutin or HAART. Nor was there a significant association with higher $CD4^+$ lymphocyte counts defined as any increase above the patient's prior lowest level or as stratified according to an absolute level greater than 50, 100 or 150 cells/μl.

Seven patients presented between 4 and 10 weeks after induction with cidofovir (three to six infusions) and one presented after 8 months of treatment. Table 2 shows the features of anterior uveitis in cidofovir-treated patients. The uveitis was bilateral in 7 of the 8 patients.

Table 1. *Numbers of patients on cidofovir, rifabutin or HAART who developed anterior uveitis*

		Patients with uveitis		
Drug	No. of patients	No.	%	p value[a]
Cidofovir	9	8	89	< 0.05
Rifabutin	5	3	60	1.00
HAART	22	12	55	0.58

HAART, highly active anti-retroviral therapy.
[a]By Yates' corrected chi-squared test.

Table 2. *Features of anterior uveitis in cidofovir-treated patients*

	No. of patients (n = 8)
Bilateral	7
Unilateral	1
3+ cells	1
2+ cells	3
1+ cells	3
Posterior synechiae	4
Keratic precipitates	1

Six of the 8 cidofovir-treated patients with anterior uveitis had bilateral CMV disease. One patient with unilateral (inactive) CMV disease developed bilateral uveitis following cidofovir treatment. In only 1 patient was the CMV retinitis clinically active at the onset of uveitis. In 4 patients there was an early rapid formation of extensive posterior synechiae with subsequent iris transillumination defects. All patients with anterior uveitis were treated at presentation with topical corticosteroids and mydriatics. The cellular anterior chamber activity resolved with topical steroid administration in all eyes with uveitis but tended to recur on withdrawal of steroids. Significant flare persisted despite topical steroids in 3 patients. The posterior synechiae responded poorly to topical mydriatic therapy, resulting in inadequate mydriasis which significantly limited the fundal view.

In 1 of the 9 cidofovir-treated patients there was a progressive reduction in intraocular pressure to less than 5 mmHg, resulting in unilateral hypotonous maculopathy with reduction of acuity to 6/18. Following cessation of cidofovir therapy in this patient the intraocular pressure initially increased with an improvement in the maculopathy, but subsequently fluctuated between 4 mmHg and 8 mmHg. The association of cidofovir with hypotony in this small series was not statistically significant.

Intravenous cidofovir treatment was discontinued in one additional patient, primarily as a result of renal toxicity. Although this patient had persistent posterior synechiae there was no evidence of active anterior uveitis 4 weeks later.

Discussion

Anterior uveitis occurred in 8 of 9 (89%) cidofovir-treated patients compared with 26% previously reported.[15] Although this small descriptive study offers little evidence of causality the association is strong and there was a clear temporal relationship in the majority of cases. Evidence supporting the role of cidofovir in uveitis includes the dose-dependence of uveitis following intravitreal injection[13] and the protection against uveitis with the use of probenecid.[12] Probenecid reduces the risk of renal toxicity due to cidofovir by reducing its peak concentration in the proximal tubule, and may have a similar protective effect on the ciliary body.

In this series cidofovir was the only significant risk factor identified but the aetiology of anterior uveitis in this group of patients may be multifactorial. Although

we did not find an association with the use of rifabutin or HAART, or with higher $CD4^+$ lymphocyte counts, the study is small and does not exclude factors that may have been identified had the number of patients been greater. Rifabutin is well known to cause uveitis,[17] especially with concomitant clarithromycin or fluconazole.[18] The risk of uveitis in cidofovir-treated patients has been associated with HAART;[15] increased immunocompetence may predispose to uveitis by enhancing inflammatory responses. Anterior uveitis is an atypical feature of active CMV retinitis itself,[19] but in only 1 of 8 cidofovir-treated patients in this study was the CMV retinitis active at the onset of the uveitis.

The uveitis developed after three to six infusions of cidofovir in 7 of the 8 patients. The uveitis mainly affected eyes with previous CMV disease, although one patient with unilateral inactive CMV disease developed bilateral uveitis. The breakdown of the blood–retinal barrier induced by CMV retinitis may increase the concentration of the systemic drug and make eyes with previous disease more likely to develop toxic reactions than eyes with intact barriers. The uveitis was typically bilateral, moderately severe, non-granulomatous and characterised in 4 cases by the early and rapid formation of extensive posterior synechiae. Treatment with topical corticosteroids controlled the cellular anterior chamber activity in all cases and continued steroid treatment was required to prevent recurrences while cidofovir therapy was continued. After the onset of the uveitis, any effect of sequential infusions of cidofovir on its intensity was masked by this treatment, but there was no suggestion of a tendency for the uveitis to become less aggressive with time. Despite initiation of topical mydriatic therapy at presentation, established posterior synechiae responded poorly and inadequate mydriasis resulted in a significantly limited fundal view. This presented considerable problems in monitoring the activity and progression of CMV retinitis.

Intravitreal injection of cidofovir can cause irreversible visually significant hypotony[10] and is associated with ciliary body atrophy on ultrasound biomicroscopy.[11] This effect may be analogous to the secretory toxicity of cidofovir in the proximal tubule of kidney. The guinea pig eye shows a similar reduction in intraocular pressure after intravitreal cidofovir and the ciliary body changes are dose-dependent.[20] The patient in this series with hypotonous maculopathy responded to withdrawal of intravenous cidofovir therapy by an increase in intraocular pressure and improvement of the maculopathy, although the intraocular pressure subsequently fluctuated between 4 mmHg and 8 mmHg. Although one study found no change in intraocular pressure with intravenous cidofovir,[21] others have reported a 50% reduction in intraocular pressure in up to 5% of patients treated.[15] Intraocular pressures in patients with HIV infection are lower than normal, however, correlating with both $CD4^+$ lymphocyte count and the extent of CMV retinitis.[22] This difference is of importance, not only because the reference range in these patients is lower but also because any further reduction in intraocular pressure carries a greater risk of hypotony and visually significant maculopathy.

Patients treated with intravenous cidofovir for AIDS-related CMV retinitis are at significant risk of visual loss due to anterior uveitis and hypotony. The use of cidofovir should be avoided in patients at increased risk of blood–aqueous barrier or blood–retinal barrier breakdown, including those with pre-existing anterior uveitis or vitritis, patients on rifabutin, and those with a good response to HAART therapy. It should also be avoided in patients with prior low intraocular pressure. Where cidofovir is used, patients should be advised to attend for urgent review in the event of pain, photophobia or visual disturbance. In the event of anterior uveitis or hypotony the need for cidofovir treatment should be reassessed. Cidofovir may be continued cautiously, possibly with reduced frequency of administration or reduced dosage (e.g. 3 mg/kg) and with careful monitoring of anterior chamber activity and intraocular pressure. Prompt intensive treatment with topical corticosteroids may control the uveitis in some patients. In the event of uncontrolled anterior uveitis or a marked reduction in intraocular pressure cidofovir should be discontinued in favour of an alternative anti-cytomegaloviral agent. Despite its adverse effects, intravenous cidofovir is effective, well tolerated, enables infrequent administration and obviates the need for an indwelling venous catheter. With careful management its potential ocular and systemic toxicity can be minimised and it remains an additional option in the treatment of CMV retinitis.

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