VISUAL PROGNOSIS OF AIDS PATIENTS WITH CYTOMEGALOVIRUS RETINITIS

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SUMMARY

A prospective study of visual acuity (VA) was performed in a cohort of 147 AIDS patients with cytomegalovirus retinitis (CMVR). Patients were treated according to standard regimes, and corrected VA was recorded at regular intervals from presentation until death. Follow-up was 6 weeks to 5 years (mean 30 weeks). Fifty patients (34%) had bilateral CMVR at initial presentation; at death 81 patients (55%) had bilateral disease. Thirty-one eyes initially uninfected developed CMVR during follow-up. Of 228 infected eyes, VA at presentation was 6/12 or better in 182 eyes (80%) and 6/60 or better in 215 eyes (94%) At death, VA was 6/12 or better in 112 eyes (49%) and 6/60 or better in 171 eyes (75%). VA in the better eye at death was 6/12 or better in 113 of 147 patients (77%), 6/24 or better in 135 patients (92%) and worse than 6/60 in only 7 patients (5%). Treatment of AIDS-related CMVR minimises loss of vision and may protect previously uninfected eyes, prolonging visual independence.

Cytomegalovirus retinitis (CMVR) is a commonly occurring opportunistic infection in patients with the acquired immune deficiency syndrome (AIDS). CMVR has been reported in up to 34% of adult patients with AIDS[1] and if untreated almost inevitably leads to blindness in affected eyes.[2,3] Survival of patients with AIDS has been steadily increasing since the condition was first described approximately 13 years ago;[4,5] this has been attributed to recent advances in anti-viral and anti-retroviral treatment for AIDS and its consequent infections.[6–8] There has been a parallel reduction in the visual morbidity from CMVR during this period,[9,10] and it is now possible for loss of vision in an affected eye to be arrested at an early stage. Nearly normal central visual acuity (VA) and even field of vision may therefore be preserved in patients with CMVR.

Most work in this field has been performed in North America, where AIDS was originally described and where AIDS-related CMVR was first recognised.[9] Although there is now also broad experience of AIDS-related CMVR in Britain, there are no large reported series in the British literature on this subject. Moreover, few recent studies world-wide have investigated the precise effects upon visual survival of recent advances in the treatment of AIDS and opportunistic infection. We have therefore performed a prospective study to assess the prognosis for vision in AIDS patients with CMVR, using current management regimes.

METHODS

Consecutive patients who presented with CMVR to St Mary's Hospital, The Western Eye Hospital and St Thomas' Hospital, London, over a 3 year period were identified prospectively. Patients who fulfilled the 1987 CDC criteria for the diagnosis of AIDS[11] and who gave informed consent to standard methods of treatment for CMVR, were enrolled in the study. Patient demographic data and examination findings were recorded on a database.

CMVR was diagnosed by clinical examination and confirmed by two experienced examiners. Patients were treated with a 2–3 week induction course of intravenous ganciclovir at a dose of 10 mg per kilogram body weight (mg/kg) per day, in two divided doses. Following reponse to initial treatment, maintenance treatment was instituted with ganciclovir at a dose of 10 mg/kg three to five times per week.[12,13] Foscarnet treatment was instituted if the patient was neutropenic, expressed a preference

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for treatment with foscarnet or if there was any other contraindication to ganciclovir treatment. The induction dose of foscarnet was 60 mg/kg three times per day for 2–3 weeks, followed by a maintenance dose of 90 mg/kg per day.

Patients with reactivation of CMVR in a previously affected eye, or infection of a previously unaffected eye, were re-induced using the same induction dosage. If CMVR was initially resistant to either drug the other was substituted wherever appropriate, and a combination of the two drugs was used if CMVR was resistant to each individual therapeutic agent. Regular haematological and biochemical analyses were performed throughout treatment to assess possible bone marrow or renal toxicity, and doses adjusted accordingly.

Patients were reviewed at 2–4 weekly intervals until death, and fundal photographs were taken through dilated pupils to assess disease progression. At every clinic visit the best corrected Snellen VA was measured in each eye before pupillary dilatation, then slit lamp examination, dilated fundoscopic examination and fundal photography were performed. Patients followed up for a minimum of 6 weeks were included in the study.

Patient survival was evaluated with Kaplan–Meier product-limit survival estimates. This technique[14] gives an assessment of the cumulative probability with time that an individual from a population will achieve a given outcome. The same technique was used to assess survival of vision (i.e. the probability that a patient's VA would not decrease below a certain level with time). The Snellen VA levels of 6/12 and 6/60 were used for assessment of visual survival.

Mean survival was calculated for sub-groups of patients for whom CMVR was and was not the first AIDS defining illness (ADI); calculation of the significance of differences between these and other groups was performed using the independent samples two-way Student's *t*-test.

The proportion of patients with best corrected VA better than or equal to the Snellen levels of 6/12, 6/24 and 6/60 was calculated at presentation and at death both for all affected eyes and for the patient's better eye. This enabled assessment of the effect of CMVR on VA in affected eyes and also on the patient's level of functional vision (i.e. corrected VA in the better eye).

Results of VA at death (or last follow-up) for all affected eyes and for all better eyes were subdivided by length of follow-up, and results were examined separately for patients who survived a minimum of 3, 4 or 6 months from initial diagnosis. The percentage of patients with VA better than the Snellen levels of 6/12, 6/24 and 6/60 were therefore compared between the groups with a minimum survival of 3, 4 or 6 months.

RESULTS

One hundred and forty-seven consecutive patients were included in the study. Of these, 136 were male homosexuals, 7 were male intravenous drug users, 2 were female intravenous drug users and 2 were female heterosexuals. CMVR was the first ADI in 16 patients (11%). The mean age at presentation of CMVR was 39 years (range 24–61 years, SD 7 years). Overall, 139 patients (95%) received treatment with ganciclovir and 45 patients (31%) received treatment with foscarnet.

Survival

During the course of the study 122 patients (83%) died. Mean life expectancy (survival) of this cohort of patients was 30 weeks after first diagnosis of CMVR (range 6 weks to 5 years, SD 34 weeks), as compared with a mean follow-up of 29 weeks (range 6–75 weeks, SD 22 weeks) in patients who did not die; this difference in length of follow-up between patients who did and did not die was not statistically significant. The mean survival of only those patients followed up for a minimum of 6 months was 54 weeks (range 27 weeks to 5 years, SD 41 weeks). The cumulative probability of survival after the first diagnosis of CMVR is shown in Fig. 1.

Mean survival was 57 weeks (range 6 weeks to 5 years, SD 75 weeks) in the 16 patients in whom CMVR was the first ADI, and 27 weeks (range 6 weeks to 2 years, SD 25 weeks) in patients in whom the ADI was not CMVR; the difference between these two groups was statistically significant ($p<0.01$). However, there was one 'outlier' in the ADI group who survived 5 years after the diagnosis of CMVR and AIDS; if this patient is excluded from the analysis the mean survival in the remaining 15 patients in the ADI group was 39 weeks (range 6 weeks to 79 weeks, SD 24 weeks) and the difference in survival between the ADI and non-ADI groups is no longer statistically significant.

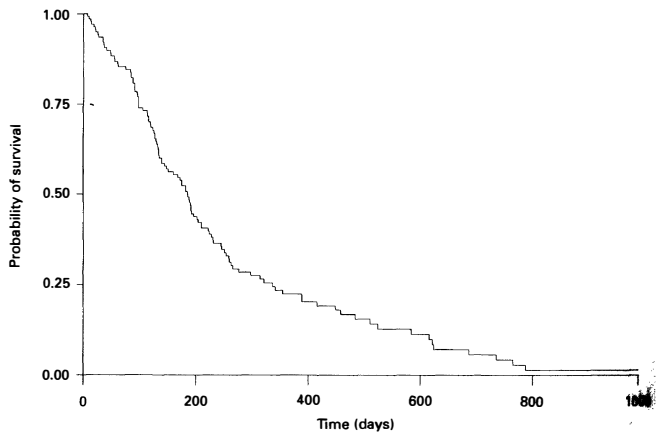

Fig. 1. *Kaplan–Meier curve showing the cumulative probability of patient survival following the diagnosis of CMVR.*

Table I. Summary of the VA results for 147 patients with AIDS-related CMV retinitis. Data are shown separately for all affected eyes and all better eyes

	n	VA≥6/12	VA≥6/24	VA≥6/60
Affected eyes				
At initial presentation of CMVR	197	156 (79%)	174 (88%)	184 (93%)
At first presentation of either eye	228	182 (80%)	204 (89%)	215 (94%)
At death (all affected eyes)	228	112 (49%)	150 (66%)	171 (75%)
Follow-up >3 months	174	85 (49%)	111 (64%)	123 (71%)
Follow-up >4 months	149	70 (47%)	90 (60%)	101 (68%)
Follow-up >6 months	114	51 (45%)	65 (57%)	70 (61%)
Better eyes				
At initial presentation of CMVR	147	135 (92%)	145 (99%)	146 (99%)
At death (all better eyes)	147	113 (77%)	135 (92%)	140 (95%)
Follow-up >3 months	107	81 (76%)	98 (92%)	101 (94%)
Follow-up >4 months	91	67 (74%)	82 (90%)	85 (93%)
Follow-up >6 months	68	50 (74%)	61 (90%)	62 (91%)

Initial Findings

At first presentation of CMVR, 197 eyes of 147 patients were affected. Reactivation of a CMVR focus present at initial retinitis presentation occurred at least once during follow-up in 87 eyes of 66 patients (45%). The mean time to this first progression was 16 weeks (range 4–59 weeks, SD 11 weeks).

The median VA in affected eyes at presentation of CMVR was 6/9 (range 6/5 to NPL) and the median VA in better eyes was 6/6 (range 6/5 to HM). Table I summarises the VA results for all patients. The VAs better than or equal to Snellen levels of 6/12, 6/24 and 6/60 in affected eyes at presentation are shown in Fig. 2.

Final Visual Acuity

During follow-up, 31 of the 97 previously unaffected ('fellow') eyes (32%) developed CMVR while receiving anti-CMV maintenance treatment. Therefore at death (or last follow-up) 66 of 147 patients (45%) kept an unaffected eye.

The median VA in all affected eyes at death was 6/18 (range 6/5 to NPL) and the median VA in better eyes was 6/9 (range 6/5 to NPL). The visual acuities better than or equal to Snellen levels of 6/12, 6/24 and 6/60 in affected eyes at death are shown in Fig. 2. The results for affected eyes at death are subdivided by minimum length of follow-up in Fig. 3.

The VA in affected eyes at death (including those which became infected during follow-up) was worse than that at presentation in 139 of 228 eyes (61%), unchanged in 56 eyes (25%) and better in 33 eyes (14%). The median reduction of VA in affected eyes between presentation and death was 2 Snellen lines (range 10 lines worse to 4 lines better, SD 3 lines). This represents a rate of visual loss of approximately 0.4 Snellen lines per month, or about 1 Snellen line every 10 weeks.

VA deteriorated before death to below 6/12 in 70 of the 182 affected eyes (38%) that had a VA of 6/12 or better at presentation, to below 6/24 in 54 of these eyes (30%) and to below 6/60 in 43 eyes (24%). The Kaplan–Meier curve of the cumulative probability with time that VA in any patient would decrease below 6/12 and 6/60 by the time of death is shown in Fig. 4. Table II summarises the causes to which reduction of VA were attributed.

VA in the better eye at death was worse than that

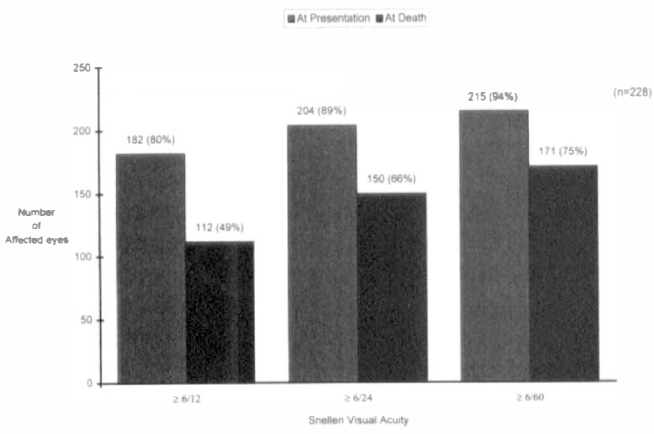

Fig. 2. *Bar graph showing the number (and percentage) of affected eyes with visual acuities at presentation and at death (or last follow-up) better than or equal to the Snellen levels of 6/12, 6/24 and 6/60 (n = 228; includes 197 eyes initially infected and 31 eyes infected subsequently).*

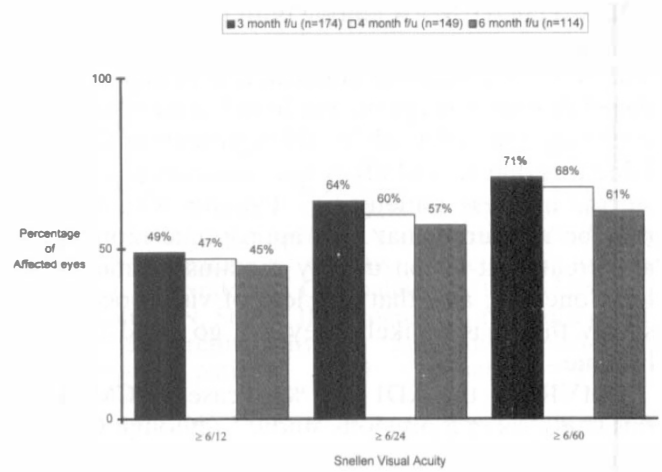

Fig. 3. *Bar graph showing the percentage of affected eyes with Snellen visual acuity better than or equal to 6/12, 6/24 and 6/60 at death (or last follow-up), subdivided by minimum follow-up (f/u) period (3, 4 or 6 months).*

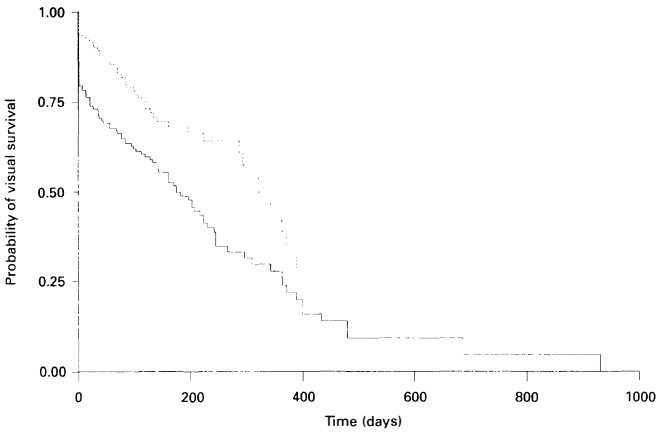

Fig. 4. *Kaplan–Meier curve showing the cumulative probability with time that Snellen visual acuity in an eye with CMVR will decrease below 6/12 (continuous line) and 6/60 (dotted line).*

at presentation in 66 of 147 patients (45%), unchanged in 63 patients (43%) and better in 18 patients (12%). The median reduction of VA in better eyes between presentation and death was 1 Snellen line (range 9 lines worse to 4 lines better, SD 2 lines).

DISCUSSION

This study represents one of the largest reported prospective evaluations of the effect of CMVR upon VA in patients with AIDS. The results confirm that with current practices it is possible for loss of VA in eyes affected by CMVR to be arrested at an early stage, and that near normal central VA in at least one eye may therefore be preserved in these patients. In this study only 5% of patients would have qualified for blind or partially sighted (BD8) registration in Britain by the time they died, on grounds of VA alone.

However, this evidence has not yet been universally assimilated, and the popular conception of AIDS-related CMVR among both the general public and patients with the condition is often of a rapidly and inevitably blinding condition. It is important to dispel this misconception, not least because suicide is a leading cause of death in AIDS patients and fear of blindness due to CMVR is the commonest cause of suicide in these patients.[15,16] Patients with CMVR may be reassured that with appropriate monitoring and treatment vision usually remains normal in at least one eye, and that any loss of vision occurs so slowly that it is unlikely they will go blind in their lifetime.

CMVR was the ADI in 11% of cases of CMVR in this study, as in a previous study,[17] although CMVR as an ADI accounts for only 2% of all cases of AIDS reported to the CDSC in the United Kingdom.[18] This difference may be because many of our cases were identified as a result of AIDS physicians screening HIV-positive patients with few or no symptoms, referring suspected cases to ophthalmologists for definite diagnosis; this screening was performed on the basis of low CD4 counts or because of suspicious findings at one of the patient's regular fundal examinations. Patients in whom CMVR was the ADI survived longer than those in whom it was not; this may be because of early detection, or because of the absence of life-threatening systemic infections that would otherwise have earlier defined AIDS.

Table II. Causes of reduced visual acuity in 147 patients with AIDS-related CMV retinitis

Cause of reduced VA	No. of eyes ($n = 228$)
Extension of CMVR to macula	82 (36%)
Optic nerve involvement (direct or sequential)	52 (23%)
Retinal detachment	47 (21%)
Cataract (total)	8 (4%)
Cataract (silicone oil induced)[a]	5 (2%)

[a]Related to surgical repair of retinal detachment.

A previous study analysed data on patients surviving a minimum period of time (6 months) in order not to bias the results in favour of better VA at death.[10] However, the results of the present study show that similar proportions of patients maintain each level of VA irrespective of whether minimum follow-up times of 3, 4 or 6 months are used, so there is little bias introduced by not limiting the cohort to such a long follow-up. Nonetheless, the trend was for worse VA with increased follow-up, and the differences might be significant with larger numbers or with longer follow-up.

Results of VA at death in this study are better than in some previous studies; one study found a VA of no perception of light in 49% of cases within 7–21 months (mean 15 months).[10] This apparent discrepancy is partly due to differences in mean survival time between the two series (65 weeks vs 30 weeks), although the seemingly increased survival of patients in the former study was biased by the selection of only those patients who survived at least 6 months; in our study the mean survival of patients followed up for a minimum of 6 months was 54 weeks. The mean survival of patients in the ganciclovir-treated arm of the SOCA trial was similar to that in our study (36 weeks vs 30 weeks).[5]

CMVR was unilateral at presentation in 97 patients (66%), which is comparable to previous reports.[17,19] Contralateral infection developed in 31 of our patients while on anti-CMV treatment.

Progression of CMVR is slower in eyes treated with anti-viral medications;[3,20] the time to first CMVR progession of 16 weeks in the present study is similar to that in previous studies.[5,19,21] We found that the majority of visual morbidity was due to extension of CMVR to involve the macula or optic nerve, which may be expected to be reduced by slowing retinitis progression; loss of vision may therefore be delayed by early detection, prompt treatment and regular monitoring.

Early detection of CMVR may be facilitated by patient education with regard to likely ocular symptoms and regular screening of at-risk patients – for example those patients with low CD4 counts, because CMVR is uncommon in patients with CD4 counts above 50 cells/mm^3.[22,23] Prompt treatment of CMVR may also be expected to preserve field of vision by limiting the total area of retina that is affected; our policy at St Mary's Hospital is to treat any area of CMVR, even in the far retinal periphery.

VA alone was used as a measure of morbidity in this study, but these patients also suffer impairment of other aspects of visual function such as field of vision,[24] stereoscopic vision and contrast sensitivity.[25,26] VA in the patient's better eye was considered, similar to binocular VA, in order to assess the effect of CMVR upon the quality of patients' functional vision.

Acuity of vision was measured in Snellen lines to allow comparison with previous studies; despite its advantages, Snellen acuity is still the most familiar and commonly used format for recording VA and is being used in many current multi-centre clinical trials. Other, more scientific measures of VA such as the Logmar test might be usefully employed in future studies, perhaps in addition to Snellen for comparison purposes.

In conclusion, early and active treatment of CMVR may delay deterioration of functional vision and protect previously uninfected eyes. In our experience, few patients with CMVR now go blind in both eyes; visual independence and quality of life may therefore be preserved throughout the natural course of the disease.

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Key words: AIDS, Cytomegalovirus retinitis, Prognosis, Survival, Visual acuity.

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