Title

Comparing treatment of acute retinal necrosis with either oral valaciclovir or intravenous aciclovir.

Authors

Julijana Baltinas[1]

Sue Lightman[1,2]

Oren Tomkins-Netzer[1,2,3]

[1] Moorfields Eye Hospital, London, UK;
[2] UCL Institute of Ophthalmology, London, UK
[3] Technion – Israel Institute of Technology, Haifa, Israel.

Correspondence:
Dr Oren Tomkins-Netzer
UCL / Moorfields Eye Hospital, City Road, London, UK. EC1V 2PD
E-mail: o.tomkins-netzer@ucl.ac.uk
Phone: +44 20 7566 2266
Fax: +44 20 7251 9350

Short title: Oral versus intravenous treatment for acute retinal necrosis

Introduction

Acute Retinal Necrosis (ARN) is a rapidly destructive form of infectious uveitis caused by Herpes zoster (VZV) and simplex virus (HSV) with an estimated incidence in the UK of up to 0.63 cases per million. [1,2] The first reports of ARN in the literature described it as a unilateral or bilateral disease with uveitis, retinal periarteritis, peripheral necrosis and retinal detachment. [3,4] Culbertson and colleagues first proposed a viral etiology for ARN in 1982 by identifying herpetic viral particles in an enucleated eye. [5] Aciclovir, an inhibitor of viral DNA polymerase, soon became the standard treatment for this condition.[6] This treatment was administered via the intravenous route at a dose of 10mg/kg every 8 hours for approximately one week to achieve adequate intraocular concentrations, and was typically followed by several months of oral therapy. [7,8] However, despite antiviral treatment reducing fellow eye involvement, rates of severe vision loss and retinal detachment (RD) in the affected eye were still high. [9-14]

The availability of newer antiviral medication with higher oral bioavailability—especially the pro-drug of aciclovir known as valaciclovir—has recently led to a shift in practice with ARN now commonly managed on an outpatient basis using oral valaciclovir. [9,15,16] This paper addresses the need, identified in Schoenberg's recently published review of the literature,[16] for studies comparing intravenous versus oral treatment in the management of ARN. Additionally, we looked at the effect of intravitreal foscarnet and barrier laser to prevent retinal detachment.

Methods

This was a large retrospective case series aiming to identify all cases of ARN at Moorfields Eye Hospital over the last two decades. Ethics approval was obtained prior to commencement (Reference: ROAD16039, causes of visual loss in patients with uveitis). ARN patients were identified by searching the electronic database for the keywords "Acute Retinal Necrosis" and "ARN" and reviewing medical records for all patients who had a previous pathology request for HSV or VZV PCR on an intraocular fluid biopsy. Although these databases only commenced in 1999, it was possible to identify ARN cases as early as 1992, where ARN was listed as a prior diagnosis. Where possible, original medical records were then obtained for all suspected cases of ARN and detailed information was collected about patient demographics, time a diagnosis of ARN was suspected or made (presentation), investigations, treatment modality, visual acuity at each visit and complications. Cases were excluded if there was insufficient detail or follow up (< 150 days), the diagnosis was revised, or the patient was not treated with either intravenous aciclovir or oral valaciclovir. Cases included had a diagnosis of ARN made clinically with confirmation by polymerase chain reaction (PCR) where possible, adequate details about presentation and treatment and a minimum follow up duration of 150 days. The choice of drug was based on the treating ophthalmologist's preference and not on clinical disease severity.

The Snellen best corrected visual acuity (BCVA) measured at each visit was directly converted to the LogMAR visual acuity scale. Where vision was assessed as count fingers, hand movements, light perception or no light perception, LogMAR values of 2.0, 2.3, 2.6 and 2.9 were assigned respectively. [17,18] Severe vision Loss (SVL) was defined as best corrected visual acuity of LogMAR ≥ 1 (or 20/200).

Data were compiled in Excel and statistical analysis was performed using Stata statistical software (version 14). Chi square and two tailed student's t-tests were performed to compare means. Multivariate linear regression using the general estimating equation was performed to assess the effect of treatment modality (intravenous aciclovir vs. oral valaciclovir) on repeated cross sections of visual acuity readings, accounting for bilateral disease. Survival analysis using Kaplan Meier survival curves and the log-rank test was conducted to analyze retinal detachment based on treatment accounting for length of follow up. Logistic regression techniques were employed to evaluate factors associated with severe vision loss and calculate odds ratios. When analyzing delay as a predictive factor for severe vision loss, delay was defined as any time elapsed from presentation to delivery of antiviral treatment exceeding one day. Analysis on number of days of delay was performed using log-transformed delays to account for the fact that delay does not continue to worsen outcomes in a linear fashion. A p value of less than or equal to 0.05 was considered significant. Data are presented as mean ± standard error of the mean (SEM), or, where specified, as mean ± standard deviation (SD) or median and interquartile range.

Results

The database search identified 203 patients with possible ARN, of which 141 were excluded on review of the detailed electronic or paper records due to inadequate detail about treatment and presentation, inadequate follow up, or an alternative final diagnosis.

In this study we included 62 patients (45% female) and 68 eyes that met the inclusion criteria; key demographic features for these cases are summarized in Table 1. The date of ARN diagnosis for the included eyes ranged from 1992 to 2016. Eyes treated initially with intravenous aciclovir dated from 1992-2015, while more recent cases from 2007-2016 were treated predominantly with oral valaciclovir with no intravenous therapy. There were 6 patients with bilateral involvement (12 eyes) and 56 patients with unilateral disease. The average patient age at time of ARN diagnosis was 48.4 ± 2.55 years. The ethnicity of patients with ARN in this cohort was 55% (34/62) Caucasian, 13% (8/62) African, 11% (7/62) South Asian, 5% (3/62) Afro-Caribbean and unknown or other in 16% (10/62) of patients. 18% (11/62) of patients were immunocompromised either due to immunosuppressive medication, or an underlying systemic disease including Human Immunodeficiency Virus (HIV). There was only partial information regarding duration of symptoms before presentation (data not shown). Overall the median time from presentation to treatment (delay) was 1.5 days (IQR 0-6), with no difference between those in the intravenous and oral groups (median 2 days, IQR 0-6 vs. median 1 day, IQR 0-11, p=0.64). On average, eyes received 1.88±0.26 (range 0-7) intravitreal anti-viral injections.

Of the eyes with ARN, 32% (22/68) were diagnosed on clinical appearance alone, while 56% (38/68) had a diagnosis of VZV ARN confirmed on PCR testing and the remaining eyes (12%, 8/68) had HSV ARN. 21% (8/38) of eyes with a positive PCR for VZV also had co-positivity for Epstein Barr virus (EBV). Of the 8 eyes with HSV, 50% (4/8) were due to HSV-1, 3 were due to HSV-2, the HSV subtype was not specified in one eye, while 2 eyes were also positive for EBV. The average age of patients at the time each eye was diagnosed with HSV ARN (27.4 years±5.4) was significantly lower than among eyes with VZV related ARN (53.6±3.25 years,

p=0.001) and the average age of those with a clinical diagnosis alone (47.8±4.14 years, p=0.01). There was no significant difference in the proportion of male patients between the group with HSV confirmed ARN (n=3, 38%) and either those with a clinical diagnosis alone (n=9, 45%, p = 0.73) or the group with VZV related ARN (n=22, 65%, p=0.17).

Overall, 33 patients with 39 affected eyes were treated with intravenous aciclovir for a median of 10 days (IQR 7-12). The dose of intravenous aciclovir was 10mg/kg, administered every 8 hours, for all but one patient. This patient was initially given 5mg/kg of aciclovir every 8 hours for the first 6 days, before the dose was increased to 10mg/kg for the subsequent 7 days. All of these patients were subsequently discharged on oral aciclovir or oral valaciclovir for a median duration of 100 days (IQR 73-307). 33% (13/39) of eyes receiving intravenous aciclovir also received adjunctive intravitreal anti-viral injections of either foscarnet or ganciclovir. 9 eyes (23%) received one injection and 4 (10%) more than one. 29 patients (29 eyes) were treated with oral valaciclovir for a median duration of 132 days (IQR 92-196). All patients were treated initially with two grams of valaciclovir taken orally every 8 hours, except for two patients who were prescribed one gram at the same dosing interval due to renal impairment in one case and clinician preference in the other. In addition, 66% of eyes (19/29) received intravitreal foscarnet injections, 10 (34%) received one injection and 9 (31%) more than one. The median follow up duration was significantly longer (p=0.05) for the intravenous treatment group (7.1 years, IQR 2.6-13.1) compared to the oral group (3.3 years, IQR 1.4-4.4), reflecting the fact that oral treatment has only been used more recently.

As can be seen in Table 1, there was no significant difference between the average age, gender or number of immunosuppressed patients between the two treatment groups. The intravenous treatment group, however, was more likely to have a clinical diagnosis without confirmatory PCR testing (p=0.02), resulting in a significantly lower proportion of eyes with PCR confirmed VZV ARN compared to in the oral group (p=0.004).

Visual Acuity

The main purpose of this study was to determine whether outpatient treatment using oral valaciclovir was comparable to traditional inpatient treatment with intravenous aciclovir. Our key finding is that there was no significant difference in final BCVA between the two treatment groups (p=0.19) or in change in BCVA from diagnosis over 5 years of cohort data (p=0.16, Figure 1), suggesting that oral valaciclovir is clinically equivalent to intravenous therapy in terms of visual acuity outcomes. Best corrected visual acuity at diagnosis was not significantly different across the two groups (1.01 LogMAR for the intravenous group versus 0.83 LogMAR for the oral group, p=0.37). On average, visual acuity for eyes in the intravenous group improved slightly at one month (to 0.78 LogMAR), but deteriorated to below the starting point by 3 months (1.14 LogMAR) and remained static from this point onwards. In contrast, the average BCVA for eyes in the oral group remained stable at one (0.88 LogMAR) and 3 months (0.90 LogMAR), but then slowly deteriorated from 6 months onwards. Visual acuity at final visit was similar for eyes in both the intravenous and oral groups (1.14 vs. 1.26 LogMAR, p=0.19). When controlling for starting BCVA, there was no significant difference seen with using oral rather than intravenous therapy on visual acuity at 3 months (p=0.77), 6 months (p=0.10), 1 year (p=0.07) or 5 years (p=0.23). In the intravenous group, 54% of eyes saw a deterioration of 3

lines or more from diagnosis to final visit while 15% saw an improvement of 3 lines or more. In the oral group, 69% of eyes deteriorated by 3 lines or more and 10% improved by the same amount. These rates of deterioration (p=0.14) and improvement (p=0.54) were not significantly different between the two treatment groups.

We performed subgroup analysis to evaluate the effect of the significantly higher number of eyes receiving adjunctive intravitreal therapy in the oral valaciclovir group. There was no significant difference in final best corrected visual acuity for patients receiving this dual therapy compared to patients on oral treatment alone (1.33 versus 1.14 LogMAR, p=0.66).

Severe vision loss of LogMAR ≥1.0 at final visit was seen in 51% (35/68) of eyes with ARN. Rates of severe vision loss were similar for eyes treated with intravenous aciclovir (46%) and oral valaciclovir (59%), with no significant difference when controlling for visual acuity at diagnosis (p=0.18). Good vision, defined as better than 20/50[19], was preserved in 29% (20/68) of eyes with similar rates of good vision at final visit for both intravenous (28%) and oral (31%) treatment groups (p=0.80).

Retinal Detachment

We found that oral valaciclovir treatment is clinically equivalent to intravenous therapy in terms of retinal detachment risk. Retinal detachment occurred in 63% (43/68) of all eyes and, controlling for adjunctive intravitreal injection, there was no difference in the rate of retinal detachment between the two treatment groups (p=0.67, Figure 2). Similar rates of retinal detachment were seen regardless of treatment delivery, occurring in 62% (24/39) of eyes with intravenous treatment and 66% (19/29) of eyes with oral treatment. Addition of an intravitreal agent to oral or intravenous treatment did not affect the retinal detachment rate (p=0.80). Median time from diagnosis to retinal detachment for the whole group was 56 days (IQR 27-113), 55 days (IQR 24-78) for the intravenous group and 63 days (IQR 32-195) for the oral group. There was also no difference in retinal detachment rate comparing eyes that received intravitreal adjunctive therapy (21/32 eyes, 66%) versus those that did not (22/36 eyes, 61%), p=0.79.

Prophylactic barrier laser was applied to 31% (21/68) of eyes in the entire cohort at a median time of 8 days post ARN diagnosis (IQR 7-19). The rate of barrier laser was similar in both the intravenous group (n=12, 41%) and the oral group (n=9, 31%). Overall barrier laser did not reduce the rate of retinal detachment, with 62% of eyes (n=13) that underwent treatment progressing to retinal detachment, (median time to detachment 56 days, IQR 35-114) compared to 64% (n=30) among those that did not have barrier laser treatment (median time to detachment 55 days, IQR 21-107) (p=0.66). There was no difference in the rates of developing retinal detachment following barrier laser between eyes in the intravenous group (n=6, 50%) and the oral group (n=7, 78%) (p=0.10). Similarly, there was no difference between the groups among those not treated with barrier laser (n=18, 67% vs. n=12, 60%, respectively) (p=0.54).

Additional Complications

A high rate of ophthalmic complications was observed in the included eyes with ARN. In addition to retinal detachment the most common complication was development of cataract in 71% of eyes (48/68, median time to develop cataract 385

days, IQR 226-583). Other common sequelae included epiretinal membrane formation (ERM) in 35% of eyes (24/68), recurrent acute anterior uveitis in 25% (17/68), and cystoid macular edema (CME) in 28% (19/68). 19% (13/68) developed hypotony and phthisis and was seen in both eyes with a history of retinal detachment (23% or 10/43) and without (12% or 3/25). Band keratopathy, corneal edema or decompensation occurred in 6% of eyes, all of which had a history of retinal detachment surgery with silicon oil. Smaller numbers of eyes were affected by glaucoma (4%), optic neuropathy (1%) and scleritis (1%). 15% of eyes (10/68) experienced a relapse with either reactivation in the same eye or involvement of the fellow eye. Among those that relapsed, 40% (4/10) were receiving prophylactic antiviral treatment. Table 2 shows ocular complications in affected eyes after treatment of ARN. Complications rates were not significantly different for patients with unilateral involvement between both treatment groups. All patients with bilateral involvement were treated with intravenous aciclovir.

Risk Factors for Severe Vision Loss

Fifteen potential risk factors were tested for severe vision loss at final visit, controlling for BCVA at diagnosis. Of these, only two factors other than starting BCVA (p=0.002) were significant: retinal detachment (p=0.01) and log-transformed delay in treatment (p=0.05). Regressing on these three variables together yielded jointly significant results (p=0.01), summarized in Table 3. The odds of severe vision loss were 4.5 times higher for a patient with retinal detachment and 3.8 times higher for a patient with a BCVA of 20/200 at diagnosis compared to one with 20/20. ARN patients with a delay of 5.2 days (mean delay) from presentation to treatment had a 2.3 times higher odds of severe vision loss than for patients with no (≤1 day) delay.

Other factors which did not have a significant association with severe vision loss at final visit included VZV, HSV, age at diagnosis, immunosuppression, presence of disc swelling, development of CME, ERM, intravitreal injection and presence of any delay to treatment (disregarding delay duration).

Discussion

The purpose of this study was to assess whether treating ARN with outpatient oral valaciclovir yielded comparable outcomes to standard intravenous aciclovir therapy. As noted in a recent literature review,[16] no prior studies have been published which directly compare outcomes with these treatment modalities for ARN. However, current practice is shifting towards managing ARN with oral valaciclovir based on good outcomes reported in small case series,[20-23] evidence that oral valaciclovir produces comparable plasma concentration to intravenous aciclovir,[24,25] and the advantages of patient convenience and lower cost as outpatient versus inpatient treatment.

The demographic features of ARN patients treated with intravenous aciclovir compared to those treated with oral valaciclovir were similar in terms of age, gender and immune status. Reflecting shifting practice, the patients treated with oral valaciclovir without intravenous therapy only included patients treated within the last ten years, while the intravenous group included patients seen over the last 25 years. However, there was no difference in the results when examining only ARN patients from the past decade (data not shown). The higher percentage of eyes with a clinical diagnosis alone in the intravenous group (and, consequently lower rate of eyes with PCR confirmed VZV ARN) might be explained by the fact that intraocular fluid

aspiration and PCR was not performed as commonly in earlier practice as it is today. Given that VZV has been shown to be the most common causative agent of ARN,[9,26-28] it is likely that the majority of eyes diagnosed clinically with ARN (without confirmatory PCR), also had VZV related ARN. In accordance with the literature,[26,27] this study found that HSV related ARN occurred on average at a younger age (27.4 years) than VZV ARN (53.6 years).

This study found that there was no significant difference in long-term visual acuity outcomes for eyes with ARN treated with intravenous aciclovir compared to oral valaciclovir. This was true when comparing BCVA at multiple times points over 5 years from diagnosis, as well as with longitudinal cross-sectional analysis of change in BCVA over time. Both groups had generally poor outcomes with severe vision loss at final visit seen in half of all patients, with no significant difference between the oral and intravenous treatment groups. These findings are consistent with other studies in the literature which report severe vision loss affecting close to 50% of ARN patients despite treatment,[9,13,29] although the current study confirms this result over a substantially longer duration (median follow-up of over 4 years, compared with 6 months or less in earlier studies). The principal factors found to be associated with severe vision loss were poor visual acuity at diagnosis and retinal detachment. The odds of severe vision loss for an eye with 20/200 BCVA on presentation or if it developed a retinal detachment was quadrupole that of an eye presenting with 20/20 vision. The odds of severe vision loss for an eye of a patient with a delay from presentation to treatment were double that of an eye of a patient with no delay, reinforcing the importance of early diagnosis and initiation of anti-viral treatment. The similarity in visual acuity outcomes for intravenous and oral therapy patients was also observed in similar rates of good vision at final visit, with approximately one in three eyes in both groups achieving final BCVA of better than 20/50.

Oral and intravenous therapy had similar rates of retinal detachment, with two-thirds of eyes developing retinal detachment at a median timing of 56 days. This is in keeping with earlier studies about RD in ARN, which report RD as generally occurring within the first three months post diagnosis and affecting between 41-73% of eyes.[10-13,29,30] The role of barrier laser in preventing retinal detachment in ARN has been controversial with some studies reporting a benefit[13,31,32] and others showing no difference in RD rate.[10,29,33] The current study did not identify any difference in RD rate when barrier laser was used to try and prevent RD from occurring. There was no significant difference in the retinal detachment rate between eyes treated with and without barrier laser in the whole group or in either treatment groups.

Recent studies have found that intravitreal foscarnet may reduce the rate of retinal detachment or severe vision loss in ARN.[34,35] The results of this study did not find evidence to support these findings, with no significant difference seen in retinal detachment rates for eyes treated with adjunctive intravitreal therapy compared to those only on intravenous or oral therapy. There was also no significant difference in final BCVA for eyes treated with oral therapy alone compared to oral and intravitreal treatment.

As in other studies, it was evident that eyes with ARN develop multiple visual complications, especially cataract and retinal detachment. As mentioned above, the rates of severe vision loss and RD were similar regardless of treatment modality. The other most common sequelae associated with ARN were epiretinal membranes,

CME, recurrent anterior uveitis and hypotony/phthisis, and the rate of these complications did not differ for intravenous versus oral therapy. Finally, a small but similar percentage of ARN patients in both oral and intravenous groups developed a reactivation in the same or fellow eye.

The limitations of this study were that it was retrospective in nature and relied on the availability of patient records and accuracy of documentation. The sample size was further limited by lack of adequate follow up data for many patients. However, the long follow-up for the patients included and standardized treatment protocols offers an opportunity to examine the effect of changing treatment approaches to this condition. Patients in our study received only few intravitreal injections as adjunctive treatment, possibly representing undertreatment using local therapy. Therefore, we are unable to comment on the effect of treatment with repeat intravitreal injections and its effect on clinical outcome and retinal detachment rates. Similarly, we could not account for the extent of barrier laser performed. While eyes generally received treatment around affected areas, we cannot comment on the effect of more extensive treatment on the risk of developing retinal detachment. There may be a correlation between the extent of retina involved and the risk of developing RD or even the decision of applying barrier laser. This may introduce a selection bias in interpreting the risk of developing RD, with eyes with greater retinal involvement more likely to receive barrier laser, but also more likely to have a RD. In this study, the retinal imaging was not extensive enough to provide detailed information about the size of retinal involvement. However, the ever-growing use of wide-angle retinal imaging may provide opportunities in the future to address this issue. The lack of PCR confirmed diagnosis, mainly during the earlier years, is a further limitation, but ARN remains mainly a clinical diagnosis and response to treatment in these cases was comparable to those with a PCR confirmed diagnosis.

In conclusion, the findings of this study suggest that visual outcomes for ARN patients treated with oral valaciclovir are not different from those of patients receiving intravenous aciclovir. Overall outcomes for ARN were generally poor, and both treatment groups were found to have similar rates of severe vision loss, retinal detachment and other ophthalmic complications. Nonetheless, it is noteworthy that a substantial and similar minority of both treatment groups did retain good vision. Retinal detachment rates were not reduced with prophylactic barrier laser and intravitreal therapy did not confer any advantages to lowering RD rates. Given the comparable results for oral and intravenous treatment, oral valaciclovir can be used to treat ARN, avoiding the need for costly and inconvenient inpatient treatment.

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Figure Captions

Figure 1. Changes in mean best corrected visual acuity (BCVA, ± standard deviation) with time for intravenous aciclovir versus oral valaciclovir were not significantly different over 5 years of data (p=0.16). The average yearly BCVA was in the range of severe vision loss (≥ 20/200) for both groups and remained stable in the long-term.

Figure 2: Kaplan Meier survival curve for retinal detachment in acute retinal necrosis for intravenous versus oral therapy; controlling for intravitreal use, there is no significant difference in the occurrence retinal detachment between the groups (p=0.67).