Management of varicella zoster virus retinitis in AIDS

Ramana S Moorthy, David V Weinberg, Steven A Teich, Brian B Berger, John T Minturn, Sanjiv Kumar, Narsing A Rao, Susan M Fowell, Isaac A Loose, Lee M Jampol

Abstract

Aims/background—Varicella zoster virus retinitis (VZVR) in patients with AIDS, also called progressive outer retinal necrosis (PORN), is a necrotising viral retinitis which has resulted in blindness in most patients. The purposes of this study were to investigate the clinical course and visual outcome, and to determine if the choice of a systemic antiviral therapy affected the final visual outcome in patients with VZVR and AIDS.

Methods—A review of the clinical records of 20 patients with VZVR from six centres was performed. Analysis of the clinical characteristics at presentation was performed. Kruskall–Wallis non-parametric one way analysis of variance (KWAOV) of the final visual acuities of patients treated with acyclovir, ganciclovir, foscarnet, or a combination of foscarnet and ganciclovir was carried out.

Results—Median follow up was 6 months (range 1.3–26 months). On presentation, 14 of 20 patients (70%) had bilateral disease, and 75% (15 of 20 patients) had previous or concurrent extraocular manifestations of VZV infection. Median initial and final visual acuities were 20/40 and hand movements, respectively. Of 39 eyes involved, 19 eyes (49%) were no light perception at last follow up; 27 eyes (69%) developed rhegmatogenous retinal detachments. Patients treated with combination ganciclovir and foscarnet therapy or ganciclovir alone had significantly better final visual acuity than those treated with either acyclovir or foscarnet (KWAOV: \( p = 0.0051 \)).

Conclusions—This study represents the second largest series, the longest follow up, and the first analysis of visual outcomes based on medical therapy for AIDS patients with VZVR. Aggressive medical treatment with appropriate systemic antivirals may improve long term visual outcome in patients with VZVR. Acyclovir appears to be relatively ineffective in treating this disease.


Varicella zoster virus retinitis (VZVR) in AIDS, also known as progressive outer retinal necrosis (PORN), is a clinically distinct necrotising retinitis syndrome caused by varicella zoster virus which occurs in immunocompromised patients. It has a rapid and progressive course leading to blindness in most cases.\(^1\) At the time of presentation, eyes demonstrate minimal clinical signs of inflammation. Most patients have a progressive relentless downhill course resulting in blindness. In one recent large series of patients with PORN, 67% of eyes had final visual acuity of no light perception (NLP) after a median follow up period of 4 weeks, and retinal detachment occurred in 70% of involved eyes.\(^3\) Although these studies have looked at the course and visual outcome of patients with VZVR, they did not address differences in visual outcome of patients treated with different antiviral regimens. We have performed a review of 20 patients from six centres with the diagnosis of AIDS and VZVR. We evaluated the long term visual outcome of these patients reviewing the medical therapies that were used. To our knowledge this is the second largest reported series of patients with PORN. We report the longest follow up of patients, and have analysed for visual outcomes with different treatment strategies.

Materials and methods

We performed a review of 20 consecutive patients with the diagnosis of VZVR and AIDS from six centres between April 1991 and April 1994. These included Northwestern University Medical School in Chicago, Mount Sinai School of Medicine, New York, Methodist Hospital in Indianapolis, Retina Consultants of Texas, Austin, University of Southern California/Doheny Eye Institute/Los Angeles County Hospital, Los Angeles, and Northern Illinois Retina Ltd, Rockford, Illinois. All patients met the diagnostic criteria for PORN described by Engstrom and associates.\(^3\) Thirty nine eyes of 20 patients were included in the study. The patients and involved eyes were evaluated based on the demographic variables: age, race, sex, and presenting CD4 lymphocyte count, and the characteristics of clinical presentation: unilateral or bilateral involvement, macular or peripheral presentation, evidence of extraocular manifestations of VZV infection (see Tables 1 and 2).

Antiviral therapy at the time of presentation and subsequent addition or change in antiviral regimen were recorded for each patient. Although treatment strategies varied among investigators we classified treatment based on the maximum medical therapy used for each patient. Maximum therapy was defined, from least to most aggressive, as follows: intravenous acyclovir (at least 10 mg/kg intravenously every
The median duration of follow up of these patients was 180 days (6 months) with a range of 1.3 to 26 months. None of these demographic characteristics showed a statistically significant association with initial or final visual acuity.

Ophthalmic findings at baseline and treatment regimen for each patient are summarised in Table 2. The visual outcomes stratified by medical therapy are presented in Figure 1. The majority (15 of 20, 75%) of patients had a history of recent or ongoing VZV infections. Eleven patients had cutaneous zoster infection, one had herpes zoster ophthalmicus, two had central nervous system zoster meningitis or vasculitis, and one had disseminated zoster viraemia. Three patients had previous or concurrent herpes simplex virus (HSV) infections, two with HSV labialis and one with disseminated HSV infection. One patient (patient 14, Table 2) had cultures of her encrusted lip lesion which revealed HSV-1, and cultures and electron microscopic examination of a choroidal biopsy specimen from the more severely involved eye revealed herpes group viral particles which could not be subclassified. Patients 8 and 9 (Table 2) also underwent diagnostic vitrectomy and choroidal biopsy in one eye. The choroidal biopsy of patient 8 revealed no organisms on light microscopy and no growth of organisms on bacterial, viral, or fungal cultures. A diagnostic enucleation was subsequently performed which revealed complete retinal necrosis with no evidence of viral particles on light and electron microscopy. Diagnostic choriotreinal biopsy of the right eye of patient 9 revealed retinal necrosis and presence of VZV particles in the retina detected by immunoperoxidase staining. Some patients presented with more than one manifestation of VZV or HSV infection. Only two patients had no manifestations of extraocular VZV or HSV infections. Eleven of the 20 patients were being treated with acyclovir at the time of presentation for past or ongoing HSV or VZV infection. One patient was receiving intravenous maintenance foscarnet for inactive cytomegalovirus (CMV) retinitis. Eight patients (40%) were not

Results

Demographic data for the 20 patients is summarised in Table 1. The mean patient age was 37.5 years. There were 17 males and three females. Of the 20 patients, 10 were white, six African-American, three Hispanic, and one Asian. The median CD4 count of the 18 patients for whom it was available was 21 cells $\times 10^3$/l with a range of 1 to 168 cells $\times 10^3$/l.

Table 1 Summary of clinical characteristics of 20 patients with varicella zoster virus (VZV) retinitis

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)</th>
<th>Race</th>
<th>Sex</th>
<th>CD4 (cells $\times 10^3$/l)</th>
<th>Extravascular manifestations</th>
<th>Unilateral/bilateral</th>
<th>Time to 2nd eye involvement (days)</th>
<th>Duration of follow up (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>31</td>
<td>Black</td>
<td>M</td>
<td>4</td>
<td>VZV</td>
<td>Unilateral</td>
<td>29</td>
<td>50</td>
</tr>
<tr>
<td>2</td>
<td>43</td>
<td>White</td>
<td>M</td>
<td>168</td>
<td>VZV</td>
<td>Unilateral</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>3</td>
<td>31</td>
<td>Black</td>
<td>M</td>
<td>8</td>
<td>VZV</td>
<td>Bilateral</td>
<td>0</td>
<td>180</td>
</tr>
<tr>
<td>4</td>
<td>28</td>
<td>Hispanic</td>
<td>M</td>
<td>21</td>
<td>VZV</td>
<td>Unilateral</td>
<td>17</td>
<td>505</td>
</tr>
<tr>
<td>5</td>
<td>35</td>
<td>Black</td>
<td>F</td>
<td>9</td>
<td>VZV</td>
<td>Unilateral</td>
<td>17</td>
<td>150</td>
</tr>
<tr>
<td>6</td>
<td>30</td>
<td>White</td>
<td>M</td>
<td>6</td>
<td>VZV</td>
<td>Bilateral</td>
<td>0</td>
<td>214</td>
</tr>
<tr>
<td>7</td>
<td>42</td>
<td>White</td>
<td>M</td>
<td>8</td>
<td>None</td>
<td>Bilateral</td>
<td>0</td>
<td>240</td>
</tr>
<tr>
<td>8</td>
<td>51</td>
<td>Black</td>
<td>M</td>
<td>3</td>
<td>VZV</td>
<td>Bilateral</td>
<td>0</td>
<td>75</td>
</tr>
<tr>
<td>9</td>
<td>38</td>
<td>White</td>
<td>M</td>
<td>39</td>
<td>VZV</td>
<td>Bilateral</td>
<td>1</td>
<td>790</td>
</tr>
<tr>
<td>10</td>
<td>37</td>
<td>Black</td>
<td>M</td>
<td>120</td>
<td>VZV</td>
<td>Bilateral</td>
<td>0</td>
<td>270</td>
</tr>
<tr>
<td>11</td>
<td>36</td>
<td>White</td>
<td>M</td>
<td>140</td>
<td>VZV</td>
<td>Bilateral</td>
<td>1</td>
<td>140</td>
</tr>
<tr>
<td>12</td>
<td>45</td>
<td>White</td>
<td>M</td>
<td>41</td>
<td>None</td>
<td>Bilateral</td>
<td>0</td>
<td>72</td>
</tr>
<tr>
<td>13</td>
<td>36</td>
<td>Hispanic</td>
<td>M</td>
<td>69</td>
<td>HSV</td>
<td>Bilateral</td>
<td>0</td>
<td>330</td>
</tr>
<tr>
<td>14</td>
<td>36</td>
<td>Hispanic</td>
<td>F</td>
<td>31</td>
<td>HSV</td>
<td>Bilateral</td>
<td>0</td>
<td>162</td>
</tr>
<tr>
<td>15</td>
<td>44</td>
<td>Black</td>
<td>M</td>
<td>&lt;500</td>
<td>VZV</td>
<td>Bilateral</td>
<td>0</td>
<td>36</td>
</tr>
<tr>
<td>16</td>
<td>32</td>
<td>Asiatic</td>
<td>M</td>
<td>160</td>
<td>VZV</td>
<td>Bilateral</td>
<td>0</td>
<td>120</td>
</tr>
<tr>
<td>17</td>
<td>55</td>
<td>White</td>
<td>M</td>
<td>38</td>
<td>VZV</td>
<td>Unilateral</td>
<td>7</td>
<td>210</td>
</tr>
<tr>
<td>18</td>
<td>27</td>
<td>White</td>
<td>F</td>
<td>4</td>
<td>HSV</td>
<td>Bilateral</td>
<td>0</td>
<td>180</td>
</tr>
<tr>
<td>19</td>
<td>46</td>
<td>White</td>
<td>M</td>
<td>1</td>
<td>VZV</td>
<td>Bilateral</td>
<td>0</td>
<td>120</td>
</tr>
<tr>
<td>20</td>
<td>31</td>
<td>White</td>
<td>M</td>
<td>31</td>
<td>VZV</td>
<td>Bilateral</td>
<td>0</td>
<td>83</td>
</tr>
</tbody>
</table>
receiving any antiviral therapy at the time of presentation.

Ocular findings at the time of presentation included bilateral involvement in 14 of the 20 patients (70%). Five of six of the unilateral cases (83%) became bilateral less than 30 days after presentation. One patient remained unilateral after 6 months of follow up. Nearly all patients (17 of 20, 85%) presented with peripheral lesions. Three patients (15%) presented with both macular and peripheral lesions. These macular lesions demonstrated characteristic whitened, necrotic parafoveal outer retina, giving the appearance of a cherry red spot. Two of these patients had bilateral foveal involvement on presentation. Two other patients presented with peripheral lesions but within 5 months of presentation developed characteristic bilateral macular lesions which did not appear to be due to contiguous spread of peripheral retinitis. Neither macular nor peripheral presentation appeared to correlate with final visual acuity (KWAOV, p = 0.37).

Control of retinitis was characterised by the lack of posterior progression and clearing of retinal opacification. Progression of retinitis was marked by new macular lesions or 200 µm or more of posterior progression of punctate white outer retinal lesions or confluent white patches of outer retinal necrosis. Both retinal drawings and photographs were utilised in determining progression. Progression was often rapid and occurred in days compared with the slower progression of cytomegalovirus retinitis. Recurrence of retinitis was marked by new macular lesions or new outer retinal, white, punctate lesions posterior to the border of previously inactive retinitis.

The medical regimen initiated was intravenous acyclovir in nine patients, intravenous foscarnet in seven, intravenous ganciclovir in one, and combination daily foscarnet and ganciclovir in three of the 20 patients. The maximum medical treatment with which patients were treated included foscarnet in nine patients, foscarnet in three patients, ganciclovir in three patients, and acyclovir in five patients. Toxicity from combination and monotherapy for ganciclovir, foscarnet, and acyclovir was not reported in any of the patients in this series. The side effects of monotherapy and combination therapy used in the treatment of CMV retinitis in patients with AIDS are well known and have been published elsewhere.5

Analysis of the initial visual acuities of the various medical treatment groups did not reveal any statistically significant differences among the four groups (KWAOV, p=0.74). Analysis of final visual acuity based on the four methods of maximum medical treatment revealed that a statistically significant difference existed among the four treatment groups. The statistical conclusions were similar when analysed for each eye (n = 39, KWAOV, p = 0.0032) and for the average of the right and left eye visual acuity for each patient (n = 20, KWAOV, p = 0.0051). As an additional confir-
mation, the amount of visual acuity loss for each eye was analysed, and a statistically similar difference between the treatment groups was demonstrated (KWAOV: p=0.0002). Subgroup analysis using KWAOV showed that treatment with combination therapy of ganciclovir and foscarnet (KWAOV, p = 0.0003) or ganciclovir alone (KWAOV, p = 0.0054) was associated with a significantly better final visual acuity than treatment with acyclovir alone. There was no significant difference in final visual acuities between the foscarnet and acyclovir treatment groups (KWAOV, p = 0.12). Nine of 10 eyes (90%) treated with acyclovir alone had final vision of NLP, whereas 10 of 29 eyes (34%) treated with other antivirals had final vision of NLP (χ², p = 0.0078).

Twenty seven eyes (69%) developed rhegmatogenous retinal detachment (RRD) a median of 30 days after presentation. The frequency of retinal detachment was similar among the four treatment groups (χ², p = 0.77). Fifteen eyes underwent intraocular surgery to repair the detachment; 14 eyes underwent pars plana vitrectomy with internal silicone oil tamponade and one eye underwent pars plana vitrectomy with intraocular gas tamponade. Two of the 14 eyes that had vitrectomy with silicone oil required two procedures each to keep the retina attached. In addition, five eyes underwent laser barrier photocoagulation for macular sparing localised RRDs. Seven eyes did not have surgical repair of RRDs because of associated systemic illnesses or the expectation of poor visual outcome because of total retinal necrosis. On final follow up 13 of 15 eyes in the vitrectomy (87%) remained attached at final follow up. Two of the patients who underwent bilateral pars plana vitrectomy with silicone oil developed bilateral cataracts and underwent cataract extraction with intraocular lens implantation and had good final visual acuities in each eye. One of these patients had a visual acuity of 20/200 in the right eye and 20/60 in the left eye after bilateral cataract extraction and posterior chamber intraocular lens implantation 17 months after presentation.

Discussion

In 1987 Jabs and colleagues described three immunosuppressed patients with presumed varicella zoster retinitis. One of these patients had AIDS, cutaneous zoster, and retinitis that was poorly responsive to available antiviral therapy. Forster and colleagues later extended the earlier observations of Jabs and colleagues, and coined the term PORN in two patients with AIDS. Since then, one large series, several small series, and several case reports describing this disease have appeared in the literature. Only anecdotal information is available to assist in the medical management of this devastating disease.

PORN is frequently compared and contrasted with acute retinal necrosis (ARN). ARN is an acute necrotising viral retinitis associated with moderate to severe vitritis and retinal vasculitis that classically occurs in otherwise healthy patients. The diagnostic criteria of ARN, as enumerated by the American Uveitis Society, have been expanded to include immunocompromised patients, but exclude patients without a...
Management of varicella zoster virus retinitis in AIDS

was derived in part from the results of Studies of Ocular Complications of AIDS Research Group2 in the treatment of CMV retinitis with both ganciclovir and foscarnet, and from other authors who suggested combination antiviral therapy for the treatment of VZVR.1111 Analysis of our data suggests that therapy with combination foscarnet and ganciclovir may reduce visual loss in patients with VZVR. The small numbers of patients in the ganciclovir group and the foscarnet group make us reluctant to generalise any analysis of these groups.

Because of previous cutaneous or disseminated zoster infections, many AIDS patients are on maintenance acyclovir therapy at the time of presentation with VZVR. In our series 11 of 20 patients were receiving oral acyclovir therapy at the time of presentation. Although oral acyclovir maintenance doses against non-ocular VZV may be lower than induction doses for VZV retinitis, it is possible that the development of resistance of the VZV to acyclovir may contribute to the poor response to therapy with intravenous acyclovir. Jacobson and colleagues13 suggested that acyclovir resistance and an associated massive viraeemia may arise from an inadequate dosing regimen of acyclovir owing to poor patient compliance or poor bioavailability of the drug. Pavesio and colleagues14 have suggested that intravitreal antivirals may also be useful in the management of VZVR since high levels of ganciclovir and foscarnet can be attained in the vitreous cavity and retina. Although this was not the primary focus of our study, combined intravenous and intravitreal antiviral therapy may be an efficacious method of controlling viral replication in the early active phases of the disease. Further studies are required to determine the exact role of intravitreal antivirals in the treatment of VZVR.

The two main vision threatening complications of VZVR are extensive retinal necrosis and RRDs.1–3 Engstrom and colleagues3 have reported that 70% of 51 eyes with PORN developed RRDs, usually within 2 months of presentation. In our series, RRDs developed in 27 of 39 eyes (69%) within a median period of 30 days of presentation. Among the 20 eyes which had surgery for RRD, 14 underwent pars plana vitrectomy with silicone oil tamponade, two eyes underwent pars plana vitrectomy and intraocular gas tamponade, and five eyes underwent laser barrier photocoagulation. On final follow up, 87% of eyes that underwent pars plana vitrectomy and silicone oil tamponade for RRD remained attached. Our data indicate that surgery is capable of anatomic success and stabilisation of vision.

PORN is a viral retinitis syndrome usually caused by VZV, and perhaps HSV, that occurs in patients with AIDS. Evidence of recent or concurrent herpes zoster infections in immunocompromised patients with retinitis should suggest a diagnosis of PORN. Cytomegalovirus retinitis remains the most common opportunistic retinal infection in people with AIDS, and VZV a distant second. These two infections are distinct in their appearance and clinical course among patients with AIDS. In our series, however, three patients presented with apparent previous or concurrent HSV infections with no history or evidence of VZV infections. Despite atypical extracellular characteristics, these patients had an appearance and clinical course indistinguishable from other patients with PORN. Cutaneous HSV infections are, however, quite common in patients with AIDS. Their concurrent presence does not imply that HSV is the causative agent for PORN. Although none of the biopsy specimens from our series demonstrated HSV particles in the retina, it is still possible that, like ARN, VZV or, far more rarely, HSV may cause VZVR.

The distinguishing features of PORN include a propensity for bilateral involvement, absent or minimal inflammatory response, very rapid progression, and a poor response to acyclovir.1–4 Patients usually present with punctate peripheral lesions alone that coalesce anteriorly with or without posterior pole involvement. One report of five patients emphasised early posterior pole involvement as a feature of PORN. In our series demonstrated HSV particles in the retina, it is still possible that, like ARN, VZV or, far more rarely, HSV may cause VZVR.

The peripheral retinitis.12 We have seen these lesions occur as the presenting symptom or, later, after the initiation of medical therapy. There tends to be rapid progression of the disease over the course of days to weeks. The peripheral lesions rapidly progress posteriorly. As the peripheral retinitis burns out, retinal atrophy and retinal pigment epithelial disturbances appear. Initial perivascular involvement followed by perivascular retinal atrophy with adjacent areas of active retinitis give the appearance of perivascular clearing.

Forster1 and later Johnston and associates11 showed a poor response to intravenous high dose acyclovir. Engstrom and associates5 described 38 AIDS patients with the diagnosis of PORN. Acyclovir was used as the sole therapy in the majority of the patients. Visual acuity was NLP in two thirds of the eyes within 4 weeks of diagnosis. Our results are slightly better with final visual acuity of NLP in 49% of eyes after a median follow up period of 6 months. The better visual outcome in the current series may be due to the more frequent use of antivirals other than acyclovir. Acyclovir was used as the primary mode of therapy in 26 of 38 patients (68%) in Engstrom’s series5 compared with five of 20 (20%) patients in the present series. In our series nine of 10 eyes (90%) treated with acyclovir alone had final vision of NLP, whereas 10 of 29 eyes (34%) treated with other antivirals had final vision of NLP (χ², p = 0.0078). Most of these were treated with combination therapy. The rationale for combination antiviral therapy in VZVR
and should rarely present a diagnostic dilemma for experienced examiners.

PORN has a dismal prognosis with a propensity for bilateral involvement and severe loss of vision. Our study is unique in its relatively long follow up and in its analysis of the visual outcomes of various modes of medical therapy. This study is limited by its non-randomised, non-blinded design. However, the analysis for confounding variables, and the high statistical confidence of the analysis of visual outcomes strongly suggest that aggressive antiviral therapy improves the visual prognosis in patients with VZVR. Acyclovir appears to be relatively ineffective. We currently recommend concurrent therapy with ganciclovir and foscarnet. We hope these results will further stimulate clinical trials to improve the understanding and treatment of this disease.

This work was supported in part by an unrestricted grant from Research to Prevent Blindness Inc, New York, USA.

Management of varicella zoster virus retinitis in AIDS

Ramana S Moorthy, David V Weinberg, Steven A Teich, Brian B Berger, John T Minturn, Sanjiv Kumar, Narsing A Rao, Susan M Fowell, Isaac A Loose and Lee M Jampol

*Br J Ophthalmol* 1997 81: 189-194
doi: 10.1136/bjo.81.3.189

Updated information and services can be found at:
http://bjo.bmj.com/content/81/3/189

These include:

**References**
This article cites 12 articles, 0 of which you can access for free at:
http://bjo.bmj.com/content/81/3/189#BIBL

**Email alerting service**
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

**Topic Collections**
Articles on similar topics can be found in the following collections

- Retina (1608)
- Neurology (1355)
- Vision (627)

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/