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Ophthalmic Technology Assessment

Diagnosis and Treatment of Acute Retinal Necrosis

A Report by the American Academy of Ophthalmology

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Purpose: To evaluate the available evidence in peer-reviewed publications about the diagnosis and treatment of acute retinal necrosis (ARN).

Methods: Literature searches of the PubMed and Cochrane Library databases were last conducted on July 27, 2016. The searches identified 216 unique citations, and 49 articles of possible clinical relevance were reviewed in full text. Of these 49 articles, 27 were deemed sufficiently relevant or of interest, and they were rated according to strength of evidence. An additional 6 articles were identified from the reference lists of these articles and included. All 33 studies were retrospective.

Results: Polymerase chain reaction (PCR) testing of aqueous or vitreous humor was positive for herpes simplex virus (HSV) or varicella zoster virus (VZV) in 79% to 100% of cases of suspected ARN. Aqueous and vitreous specimens are both sensitive and specific. There is level II and III evidence supporting the use of intravenous and oral antiviral therapy for the treatment of ARN. Data suggest that equivalent plasma drug levels of acyclovir can be achieved after administration of oral valacyclovir or intravenous acyclovir. There is level II and III evidence suggesting that the combination of intravitreal foscarnet and systemic antiviral therapy may have greater therapeutic efficacy than systemic therapy alone. The effectiveness of prophylactic laser or early pars plana vitrectomy (PPV) in preventing retinal detachment (RD) remains unclear.

Conclusions: Polymerase chain reaction testing of ocular fluid is useful in supporting a clinical diagnosis of ARN, but treatment should not be delayed while awaiting PCR results. Initial oral or intravenous antiviral therapy is effective in treating ARN. The adjunctive use of intravitreal foscarnet may be more effective than systemic therapy alone. The role of prophylactic laser retinopexy or early PPV is unknown at this time. *Ophthalmology 2017;124:382-392 © 2017 by the American Academy of Ophthalmology*

The American Academy of Ophthalmology prepares Ophthalmic Technology Assessments to evaluate new and existing procedures, drugs, and diagnostic and screening tests. The goal of an Ophthalmic Technology Assessment is to review systematically the available research for clinical efficacy and safety. After review by members of the Ophthalmic Technology Assessment Committee, other Academy committees, relevant subspecialty societies, and legal counsel, assessments are submitted to the Academy's Board of Trustees for consideration as official Academy statements. The purpose of this assessment by the Ophthalmic Technology Assessment Committee Retina/Vitreous Panel is to evaluate the diagnosis and treatment of acute retinal necrosis (ARN).

Background

Acute retinal necrosis was first described in 1971 by Urayama and colleagues[1] as a syndrome of acute panuveitis with retinal periarteritis progressing to diffuse necrotizing retinitis and retinal detachment (RD) (Figs 1 and 2). It is an uncommon syndrome caused by human herpes viruses that can affect immunocompetent or immunosuppressed patients of either gender at any age. On the basis of 2 nationwide UK surveys, the annual incidence of ARN is estimated to be 0.5 to 0.63 new cases per million population.[2,3]

In 1994, the Executive Committee of the American Uveitis Society[4] defined ARN on the basis of the following clinical characteristics: (1) 1 or more foci of retinal necrosis with discrete borders located in the peripheral retina, (2) rapid progression in the absence of antiviral therapy, (3) circumferential spread, (4) evidence of occlusive vasculopathy with arterial involvement, and (5) a prominent inflammatory reaction in the vitreous and anterior chamber. Non-necrotizing and multifocal posterior necrotizing variants also have been described.[5,6] Patients presenting with anterior uveitis should undergo a dilated eye examination to assess for ARN and other causes of uveitis.

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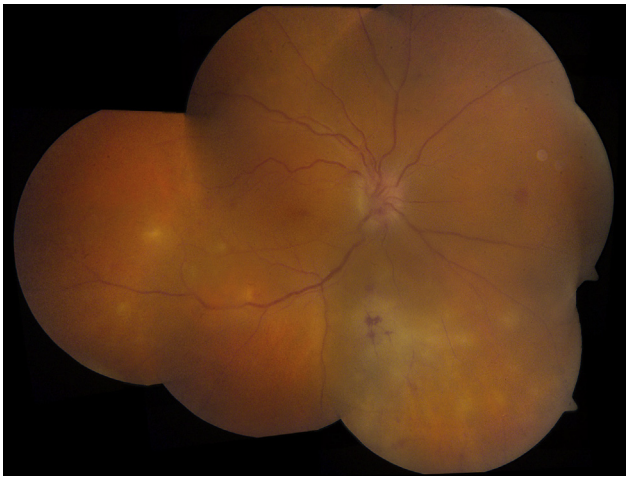

Figure 1. Montage fundus photograph of a patient with acute retinal necrosis (ARN) reveals vitritis, retinitis, retinal vasculitis, retinal hemorrhage, and optic nerve head edema. (Courtesy of Stephen J. Kim, MD.)

Culbertson et al[7] first described histologic evidence of herpetic involvement in ARN in 1982. Several laboratory studies have confirmed a herpetic cause, including polymerase chain reaction (PCR)-based techniques, serum or intraocular fluid antibody testing, viral culture, retinal biopsy, and immunocytochemistry.[8] Varicella zoster virus (VZV) is the most common cause, followed by herpes simplex virus (HSV) types 1 and 2.[3,9,10] Cytomegalovirus (CMV) and Epstein-Barr virus (EBV) also have been reported as causative agents.[8,10]

Visual outcomes are generally poor, and 48% of affected eyes have a visual acuity (VA) worse than 20/200 6 months after onset of ARN.[2] Retinal detachment is the most common cause of decreased vision; it occurs in 20% to 73% of treated eyes in more recent studies,[9,11] but rates up to 85% have also been reported.[12] Vision loss also may occur as a result of chronic vitritis, epiretinal membrane, macular ischemia, macular edema, and optic neuropathy.[9,13] Additional morbidity and mortality may occur with central nervous system or contralateral eye involvement. Bilateral ARN occurs in up to 70% of untreated patients.[14] Contralateral involvement usually occurs within a few months but may occur years later.[14,15]

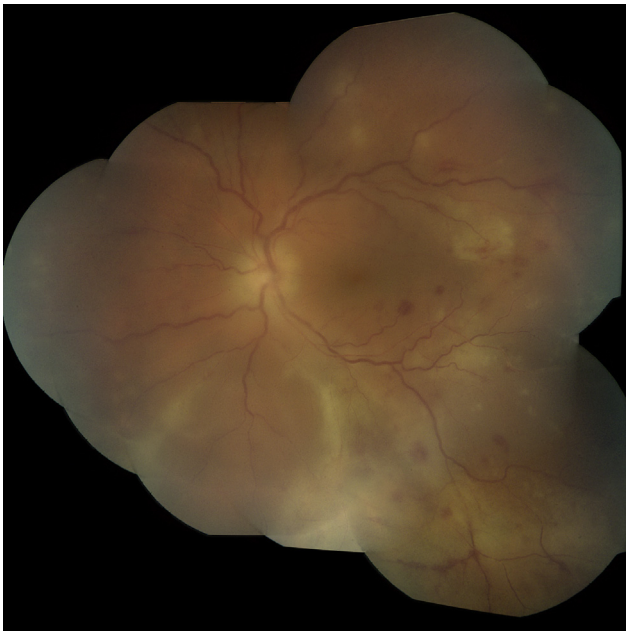

Figure 2. Montage fundus photograph of a patient with ARN reveals vitritis, multifocal and confluent areas of retinitis, retinal vasculitis, retinal hemorrhage, optic nerve head edema, and retinal detachment. (Courtesy of Stephen J. Kim, MD.)

In 1986, Blumenkranz et al[12] reported the regression of retinal lesions with intravenous acyclovir. In 1991, Palay et al[14] found a reduction in contralateral eye involvement from 70% to 13% with intravenous acyclovir. Treatment at a dose of 10 mg/kg every 8 hours or 1500 mg/m^2 per day divided into 3 doses for 7 to 10 days followed by an oral antiviral is the most established treatment regimen.[9,10,12,15] However, since the advent of newer oral antivirals (e.g., valacyclovir, famciclovir) that have greater bioavailability and the increasing adoption of intravitreal injection, multiple studies have reported successful outcomes using initial oral with or without intravitreal therapy without concomitant intravenous treatment.[15–17]

Adjunctive treatment modalities have been described, including early pars plana vitrectomy (PPV) with or without silicone oil before RD, laser retinopexy around areas of necrosis to prevent RD, systemic or local corticosteroids, and systemic antiplatelet agents.[9,15]

Acute retinal necrosis is a rapidly destructive disease that has substantial morbidity and the predilection to involve the fellow eye, but its rarity precludes the conduct of large randomized clinical trials. Consequently, clinical management largely has been guided by retrospective studies and case reports. Given recent advances in the diagnosis and the introduction of new treatments, this subject merits further review.

Description of the Intervention

Early accurate diagnosis of ARN is critical to initiate timely antiviral therapy. Multiple diagnostic methods have been reported, and many recent studies have used PCR-based techniques for rapid diagnosis. The advent of newer oral antivirals with greater bioavailability has resulted in a greater use of first-line oral therapy, which has the distinct advantage of outpatient administration at substantial cost savings. In addition, the adjunctive use of intravitreal antiviral therapy has been increasingly reported and provides immediate intravitreal drug levels that greatly exceed what can be initially achieved by systemic administration. Because of the high risk of RD with ARN, some ophthalmologists have advocated using prophylactic laser retinopexy (posterior to or surrounding the areas of the necrotic retina) and early PPV to reduce the risk of RD.[10,11]

Resource Requirements

Most treatment regimens for ARN consist of initial intravenous acyclovir therapy for 7 to 10 days.[9,10,12,15] Patients are then treated with oral therapy at the discretion of the

treating physician. The duration of treatment is typically many months and is influenced by systemic comorbidities, immune status, and laterality.

The cost of a 10-day course of oral valacyclovir 1000 mg 3 times daily, oral famciclovir 500 mg 3 times daily, and intravenous acyclovir 500 mg 3 times daily is $379.20, $303.90, and $600.00, respectively.[18–20] Intravitreal foscarnet must be compounded by a pharmacy, and thus the cost of a dose of foscarnet for intravitreal use is variable.

The average cost per inpatient day across the United States in 2011 ranged from $1628.00 to $2088.00, depending on the hospital system.[21] Therefore, the estimated cost of a 7-day hospital admission for intravenous acyclovir could range from $11 996.00 to $15 216.00, which does not include other costs associated with hospitalization (physician, imaging, laboratory, and other costs).

The 2016 Medicare nonfacility reimbursement for Current Procedural Terminology (CPT) code 67145 (prophylaxis of RD; photocoagulation) is $533.84.[22] The 2016 Medicare reimbursement for CPT code 67036 (vitrectomy, mechanical, pars plana approach) is $914.44 and for CPT code 67040 (vitrectomy, mechanical, pars plana approach; with endolaser photocoagulation) is $1058.38.

The cost of PCR testing is highly dependent on the PCR technique and the laboratory used. Estimated costs are approximately $395.00.[23,24]

Questions for Assessment

The objective of this review is to address the following questions:

1. What is the role of PCR testing in ARN?
2. Does the choice of initial management using intravenous versus oral antiviral therapy affect the clinical course and outcome of ARN?
3. Does adjuvant intravitreal antiviral therapy affect visual or anatomic outcomes?
4. Does prophylactic laser retinopexy or early PPV before RD decrease the incidence of RD and improve visual outcomes?

Description of Evidence

Literature searches were last conducted in PubMed and the Cochrane Library databases on July 27, 2016, without date or language restrictions. The search strategy used the following MeSH terms and text words: *retinal necrosis syndrome, acute [MeSH], paracentesis [MeSH], HHV patient admission [MeSH], light coagulation [MeSH], vitrectomy [MeSH], intraocular [MeSH], antiviral agents [MeSH], acute retinal necrosis, acute retinal necroses, paracentesis, antiviral agents, antiviral therapy, antiviral therapies, acyclovir, human herpes virus, patient admission, light coagulation, photocoagulation, vitrectomy, injections, intraocular injection,* and *intraocular injections.*

A total of 216 unique citations were found. The panel reviewed the abstracts of these articles and selected 49 of possible clinical relevance that then were obtained in full text. Of the 49 articles, 27 were deemed sufficiently relevant and were reviewed by the panel methodologist (J.E.T.). The methodologist used a rating scale based on that developed by the British Centre for Evidence-Based Medicine and assigned 1 of the following ratings of level of evidence to each of the selected articles.[25] A level I rating was assigned to well-designed and well-conducted randomized clinical trials; a level II rating was assigned to well-designed case-control and cohort studies, and poor-quality randomized studies; and a level III rating was assigned to case series, case reports, and poor-quality cohort and case-control studies.

Of the 27 articles reviewed, 9 were considered level II and 18 were considered level III. There were no level I studies. An additional 6 articles were identified in the reference lists of the 27 articles as articles of interest and were included. These 6 articles all assessed serum and/or vitreous drug levels after systemic antiviral administration in patients without ARN.

Published Results

Diagnosis of Acute Retinal Necrosis

Historically, the diagnosis of ARN is made by clinical examination, but underdiagnosis or misdiagnosis of less typical presentations is a concern, because delay in diagnosis often leads to poor clinical and visual outcomes. When the clinical examination is suggestive of ARN, treatment should be initiated and laboratory confirmation may not be necessary. Laboratory methods that aid in diagnosis include serum or intraocular fluid antibody testing, viral culture, retinal biopsy, and immunocytochemistry, but routine use of these methods has been limited by poor sensitivity or specificity, lack of widespread availability for testing, and excessive risk to the patient.

Polymerase Chain Reaction. Polymerase chain reaction is a method used to identify viral DNA from small aqueous or vitreous samples through enzymatic amplification of nucleic acids using DNA polymerase and specific primers. Its specificity is high; studies have shown that most eyes without herpetic uveitis test negative for the presence of herpes virus DNA, even in the presence of positive serum antibodies.[26] Polymerase chain reaction techniques make it possible to determine the specific virus type in cases of ARN.

Numerous studies have reported on PCR testing of aqueous and vitreous samples in the setting of ARN (Table 1).[2,8-10,27-35] In patients with suspected ARN, PCR testing was positive for HSV or VZV DNA in 79% to 100% of cases. Two level III studies showed a decrease in the number of viral DNA particles with antiviral treatment.[36,37] Comparisons across studies are difficult because of differences in PCR testing and laboratory techniques. Acute retinal necrosis may present with clinical features that resemble other causes, and, as reported by Knox et al[27] and Gargiulo et al,[33] a negative PCR result may lead to another diagnosis.

Of studies that tested both aqueous and vitreous levels, only 1 found a notable difference (93% positive for vitreous specimens,

Table 1. Studies Reporting Polymerase Chain Reaction Testing in Acute Retinal Necrosis

Author(s), Year	Level	Diagnosis	No. of Eyes/Patients	Sample	Positive Polymerase Chain Reaction	Notes
Knox et al[27] 1998	II	Retinitis	38 eyes of 37 patients, number with suspected ARN not clearly reported	Vitreous	24 cases positive, 14 of which were for VZV or HSV that included ARN and progressive outer retinal necrosis	All other positive cases were CMV retinitis 13 negative cases later diagnosed with other cause
Lau et al[10] 2007	II	ARN	18 eyes	Vitreous	16/18 (89%)	3 eyes positive for both VZV and EBV
Sugita et al[28] 2008	II	Uveitis	111 eyes, 16 eyes with ARN	Aqueous and vitreous	16/16 (100%)	For ARN cases, number of aqueous versus vitreous samples not specified
Yeh et al[29] 2014 and Flaxel et al[30] 2013	II II	ARN	14 eyes	Aqueous and vitreous	Total 11/14 (79%)	12 aqueous samples, 2 vitreous samples, number of positive cases within each group not reported
Itoh et al[31] 2000	III	ARN	16 patients	Aqueous and vitreous	16/16 (100%)	Number of aqueous versus vitreous samples not specified
Ganatra et al[8] 2000	III	ARN	30 eyes	Aqueous and vitreous	Total 31/33 samples (94%) Vitreous — 21/23 eyes (91%) Aqueous — 10/10 eyes (100%)	29/30 eyes had a positive PCR The only negative PCR result was a patient tested 6 wks after starting acyclovir
Tran et al[32] 2003	III	Necrotizing herpetic retinitis	22 patients, 19 patients with ARN	Aqueous	16/19 (84%)	2/16 had a positive result 1 wk after negative initial test
Gargiulo et al[33] 2003	III	Uveitis, possible ARN	11 eyes	Aqueous	5 cases positive	6 negative cases later diagnosed with other cause
Hillenkamp et al[9] 2009	III	ARN	30 eyes	Vitreous	30/30 eyes (100%)	In 3 eyes, 2 viruses were detected (VZV and EBV, 2 eyes; VZV and HSV, 1 eye)
Sims et al[34] 2009	III	ARN	14 patients	Aqueous and vitreous	Aqueous — all samples positive Vitreous — at least 1 negative result	1 patient had a negative vitreous but positive aqueous sample Number of aqueous and vitreous samples not clearly reported
Wong et al[35] 2010	III	ARN	88 eyes	Vitreous	81/88 (92%)	No further data provided on 7 negative eyes
Cochrane et al[2] 2012	III	ARN	34 patients	Aqueous, vitreous, and CSF	30/34 (88%), 3 from CSF Vitreous more likely to be positive (93%) than aqueous (46%)	Unable to remove CSF studies to analyze only ocular samples

ARN = acute retinal necrosis; CMV = cytomegalovirus; CSF = cerebrospinal fluid; EBV = Epstein-Barr virus; HSV = herpes simplex virus; PCR = polymerase chain reaction; VZV = varicella zoster virus.

46% positive for aqueous specimens).[2] Other studies found no meaningful difference between aqueous and vitreous samples.[8,34] There are insufficient data demonstrating the superiority of vitreous over aqueous sampling or vice versa. In patients with suspected ARN, treatment should not be delayed while awaiting results of PCR testing.

Antiviral Treatment of Acute Retinal Necrosis

The most frequently reported initial treatment of ARN includes intravenous acyclovir or oral valacyclovir. Other treatments include oral famciclovir, valganciclovir or acyclovir, and intravenous foscarnet or ganciclovir. Adjuvant local therapy, such as intravitreal foscarnet or ganciclovir, also may be considered. If PCR testing confirms CMV as the cause for ARN, treatment is similar to that for CMV retinitis. It may differ from treatment of ARN caused by VZV and HSV. There are insufficient published data on ARN associated with EBV to guide treatment.

Acyclovir is an acyclic purine nucleoside analogue that is converted to acyclovir monophosphate by virus-encoded thymidine kinase.[38,39] Cellular enzymes catalyze the subsequent diphosphorylation and triphosphorylation steps, which yield high concentrations of acyclovir triphosphate that inhibits viral DNA synthesis through competitive inhibition of viral DNA polymerase. Acyclovir is given orally and intravenously. Reported 50% inhibitory concentration (IC_{50}) values for HSV-1, HSV-2, and VZV are shown in Table 2.[38] Valacyclovir is the orally given prodrug that is converted to acyclovir during first-pass metabolism. Its bioavailability is 54% to 60%.[42,43] In comparison, the bioavailability of oral acyclovir ranges from 15% to 30%.[44]

Penciclovir resembles acyclovir in chemical nature, mechanism of action, and spectrum of antiviral activity.[40] Like acyclovir,

Table 2. Reported 50% Inhibitory Concentration for Acyclovir, Penciclovir, and Foscarnet[38,40,41]

	HSV Type 1	HSV Type 2	VZV
Acyclovir	0.02–13.5 μg/ml	0.01–9.9 μg/ml	0.12–10.8 μg/ml
Penciclovir	0.04–0.6 μg/ml	0.05–2.1 μg/ml	0.1–5.0 μg/ml
Foscarnet	10.0–130.0 μmol/L	10.0–130.0 μmol/L	48.0–90.0 μmol/L

HSV = herpes simplex virus; VZV = varicella zoster virus.

penciclovir is first monophosphorylated by viral thymidine kinase, and it blocks viral DNA synthesis through competitive inhibition of viral DNA polymerase. It is given intravenously. Reported IC_{50} values for HSV-1, HSV-2, and VZV are shown in Table 2.[40] Because penciclovir is poorly absorbed, the prodrug famciclovir is used clinically and given orally, and it is converted to penciclovir in the liver. Its bioavailability is reported to be 77%.[40]

Foscarnet is an organic analogue of inorganic pyrophosphate that selectively inhibits the pyrophosphate binding sites on viral DNA polymerases at concentrations that do not affect human DNA polymerases, and it can be effective in acyclovir-resistant HSV strains.[45] The reported IC_{50} values for HSV-1, HSV-2, and VZV are shown in Table 2.[41]

Serum Drug Levels. Höglund et al[43] conducted a randomized crossover study at 2 centers to assess serum acyclovir levels after administration of intravenous acyclovir or oral valacyclovir. Patients received intravenous acyclovir 5 mg/kg every 8 hours for 7 doses followed 24 hours later by crossover to valacyclovir 1000 mg every 8 hours for 7 doses, or vice versa. The mean area under the curve (AUC) was 64.2 μmol•hr/L for intravenous acyclovir and 76.3 μmol•hr/L for oral valacyclovir ($P = 0.15$). Mean maximal concentration was 34.0 μmol/L after intravenous acyclovir and 26.6 μmol/L after oral valacyclovir ($P = 0.04$). Time to maximal concentration was 1 hour for intravenous acyclovir and 2 hours for oral valacyclovir.

Weller et al[39] conducted 2 phase I studies on 60 healthy volunteers given oral valacyclovir ranging from 250 to 2000 mg 4 times daily for 11 days. Serum acyclovir levels were measured, and no patients received intravenous acyclovir. Maximal acyclovir concentration with 8000 mg daily dosing (2000 mg 4 times daily) was 8.49 μg/ml, and mean AUC was 109 μg•hr/ml. Values were comparable to those reported in the literature for intravenous acyclovir 10 mg/kg every 8 hours (maximal concentration 20.7 μg/ml, AUC 107 μg•hr/ml).[46]

Soul-Lawton et al[42] randomized 12 healthy volunteers to a single dose of 1000 mg of oral valacyclovir or 350 mg of intravenous acyclovir. Each volunteer was crossed over to the other medication after a 1-week interval. Serum acyclovir levels were measured at various time intervals. Maximal serum concentration of acyclovir was 29.53 μmol/L after oral valacyclovir and 40.99 μmol/L after intravenous acyclovir. Time to maximal concentration was 1.7 hours in the oral valacyclovir group and 1 hour in the intravenous acyclovir group. The AUC was 89.4 μmol•hr/L for oral valacyclovir and 84.0 μmol•hr/L for intravenous acyclovir.

These studies demonstrate that administration of valacyclovir (1000 mg) or intravenous acyclovir (5 mg/kg or 350 mg) results in similar serum acyclovir AUC levels. In addition, AUC levels after 2000 mg of oral valacyclovir 4 times daily were comparable to reported values for 10 mg/kg of intravenous acyclovir every 8 hours. Despite comparable AUC levels, a higher maximal acyclovir concentration and faster time to peak concentration were demonstrated with intravenous dosing.

Vitreous Drug Levels. Huynh et al[47] studied the vitreous penetration of acyclovir after administration of oral valacyclovir. Ten patients undergoing routine vitrectomy were given 3 doses of 1000 mg of valacyclovir 8 hours apart on the day before surgery and an additional dose the morning of surgery. Serum and undiluted vitreous samples were taken and analyzed for acyclovir levels. Mean serum levels were 4.41 μg/ml, and mean vitreous levels were 1.03 μg/ml. The mean vitreous-to-serum concentration ratio was 0.24.

Chong et al[48] studied the vitreous penetration of penciclovir after oral administration of famciclovir. Ten patients undergoing routine vitrectomy were given 3 doses of famciclovir 500 mg the day before surgery and another dose on the morning of surgery. Serum and undiluted vitreous samples were taken and analyzed for penciclovir levels. Mean serum levels were 4.45 μg/ml, and mean vitreous levels were 1.21 μg/ml. The mean vitreous-to-serum concentration ratio was 0.28.

All eyes in both studies were noninflamed and undergoing elective vitrectomy. Vitreous drug levels in inflamed eyes with a compromised blood ocular barrier may be higher. Although there are no human studies measuring vitreous acyclovir levels after intravenous dosing, both studies suggest that oral antiviral therapy alone achieves vitreous levels within the reported IC_{50} range for VZV, HSV-1, and HSV-2 (Table 2).[38,40]

Treatment with Intravenous Antivirals. Intravenous antiviral therapy historically has been the standard treatment for ARN, and several parameters have been used to follow the response to treatment, including the time to initial and complete regression of retinitis, visual outcomes, incidence of RD, and fellow eye involvement.

Blumenkranz et al[12] (level III) retrospectively reviewed 13 eyes of 12 patients with ARN who were treated with intravenous acyclovir 1500 mg/m^2/day for a mean of 10.9 days. Patients also received oral aspirin or warfarin, and 9 of 12 patients were treated with systemic corticosteroids. There was no control group. Follow-up ranged from 1 to 30 months (mean, 14.5 months). Regression of retinitis on average began 3.9 days after treatment initiation and was complete by 32.5 days. No patient had progression of retinitis after 48 hours. The incidence of RD (84.6%) was higher than for untreated historical controls.[49,50] Three of 11 patients (27%) with unilateral disease developed fellow eye involvement in a time period ranging from 1 to 5 years later.

Palay et al[14] (level II) conducted a retrospective comparative study of ARN managed with intravenous acyclovir versus no treatment. A total of 54 immunocompetent patients with unilateral ARN were included; 31 were treated with intravenous acyclovir 1500 mg/m^2/day for 7 to 10 days, then orally for 2 to 4 weeks (dose and frequency not specified), and the remaining 23 were not. Of the patients treated, 87% remained disease free in the contralateral eye compared with just 30% of the untreated patients. Treatment with intravenous acyclovir significantly reduced the incidence of fellow eye involvement ($P = 0.001$). Contralateral eye involvement was most pronounced during the first 14 weeks after diagnosis.

Crapotta et al[51] (level III) retrospectively reviewed 13 eyes of 12 patients with ARN. Seventy-seven percent of eyes had less

than 25% retinal involvement. Patients were treated with intravenous acyclovir 10 mg/kg every 8 hours. In 11 of 12 patients, complete resolution was seen within 21 days. Three of 13 eyes developed an RD in the follow-up time of 3 to 21 months. Visual acuity at the final follow-up visit was 20/40 or better in 46% of eyes, 20/60 or better in 62% of eyes, and 20/400 or better in 92% of eyes. Two eyes reactivated in 2 and 5 weeks, respectively, after stopping oral acyclovir. No patient developed bilateral disease.

Tibbetts et al[15] (level II) conducted a retrospective multicenter study of 58 patients with unilateral ARN. Patients were divided into the acyclovir-only era (36 eyes; 1981−1997) and the newer antiviral era (22 eyes; 1998−2008 [after valacyclovir and famciclovir became available]). All patients in the acyclovir-only era received intravenous acyclovir 500 mg/m^2 3 times daily for 7 to 10 days, followed by at least 6 weeks of oral acyclovir 800 mg 5 times daily in half of the patients, whereas the other half were not treated after completing intravenous therapy. In the newer antiviral era, 15 eyes were initially treated with intravenous acyclovir (140−1000 mg 3 times daily), 6 of which also received intravitreal antiviral therapy (foscarnet 1.2−2.4 mg in 0.1 ml or ganciclovir 200−400 μg in 0.1 ml). The other 7 eyes in the newer antiviral era were initially managed with oral antiviral therapy. In the acyclovir-only group, patients were followed for a median of 24 months, and the incidence of RD was 47%. Among the 51 patients in both groups initially treated with intravenous acyclovir, 1 (2%) developed contralateral eye involvement 37 months after initial diagnosis while on prophylactic valacyclovir 500 mg twice daily.

Treatment with Oral Antivirals. In the study by Tibbetts et al[15] (level II), 7 patients in the newer antiviral era were initially managed with oral therapy (acyclovir, valacyclovir, or famciclovir) with or without adjuvant intravitreal therapy (foscarnet or ganciclovir). Two of the patients were started on oral antiviral (valacyclovir or famciclovir, dose not specified) and switched to intravenous acyclovir, but the clinical course of these patients was not described. Initial antiviral management was at the discretion of the treating ophthalmologist, and baseline characteristics of these patients were not included. The choice of initial oral or intravenous antiviral therapy did not have a significant effect on the final VA or development of RD. One patient initially managed with oral therapy developed fellow eye involvement 8 months later while on prophylactic valacyclovir 500 mg 3 times daily.

Emerson et al[52] (level III) reviewed 6 eyes of 4 patients with ARN who were managed with oral valacyclovir 1000 mg 3 times daily or famciclovir 500 mg 3 times daily. Symptoms and VA improved in 75% of patients within 2 to 4 weeks. Two eyes developed an RD. Neither eye with unilateral involvement developed fellow eye involvement.

Aizman et al[16] (level II) reviewed 10 eyes of 8 patients with ARN who were managed with oral valacyclovir 1000 mg 3 times daily or famciclovir 500 mg 3 times daily (4 patients each). Patients were treated with oral prednisone when regression was observed. One eye received intravitreal foscarnet. Resolution was identified on examination and by means of wide-field photography. Initial response to treatment was seen as early as 4 days (mean, 6.3 days). Complete resolution was seen on average at 17 days (median, 14 days). None of the 6 patients with unilateral disease developed fellow eye involvement (follow-up 7−72 weeks). Thirty percent of eyes developed an RD.

Taylor et al[17] (level III) reviewed 10 eyes of 9 patients with ARN who were treated with oral valacyclovir. Two patients were positive for human immunodeficiency virus. Eight of the 9 patients were initially treated with valacyclovir 2000 mg 3 times daily. Follow-up ranged from 7 to 104 weeks (mean, 31 weeks). Median time to initial response was 7 days (range, 7−14 days) and to complete resolution was 21 days (range, 7−42 days). Thirty percent of eyes developed an RD. None of the patients with unilateral disease developed fellow eye involvement.

Intravenous versus Oral Antivirals. There are no studies that directly compare oral with intravenous therapy for ARN. Comparisons across studies are difficult because of the retrospective nature of the studies, differences in baseline characteristics, variable outcome measures, and different time periods being studied (intravenous therapies in the 1980s and 1990s; oral therapy in the 2000s). Despite these limitations, the body of evidence suggests that the time to initial and complete regression of retinitis appears comparable to oral or intravenous therapies. In addition, the development of contralateral eye involvement was low with both modes of therapy.

Treatment with Intravitreal Antivirals. Two comparative studies[29,35] specifically addressed the role of adjuvant intravitreal therapy in patients with ARN who were managed using systemic antivirals. Other studies also included data on intravitreal antiviral therapy as part of their review.

Wong et al[35] (level III) reviewed 104 eyes with ARN. A total of 81 eyes of 74 patients had PCR confirmation, and the remaining eyes did not have a biopsy (16 eyes) or the result was negative (7 eyes). Two study centers were included, and all patients received intravenous acyclovir for 7 to 10 days, followed by oral antiviral therapy. All patients at 1 site received a single intravitreal foscarnet injection (2.4 mg/0.1 ml) within 3 days of presentation. At the other site, intravitreal foscarnet was not given. In 48 of 81 eyes, ARN was caused by VZV, and in the remaining 33 cases, ARN was caused by HSV. Among all 104 patients, combination systemic antiviral and intravitreal foscarnet (64 eyes) was associated with a significantly reduced risk of RD (36% vs. 60%, $P = 0.03$) when compared with systemic treatment alone (40 eyes). Varicella zoster virus was associated with a 2.5-fold greater chance of RD compared with HSV. Among HSV eyes, RD developed in 25% of patients who received foscarnet and 20% in patients who did not receive foscarnet. Among VZV eyes, RD developed in 54% of patients who did receive foscarnet and 75% in patients who did not receive foscarnet ($P = 0.23$). Data on baseline VA and the extent of retinitis among patients who did and did not receive intravitreal foscarnet were not available. Median follow-up differed between the sites (16 months for those who received foscarnet vs. 85 months for those who did not).

A single-center, interventional retrospective comparative case series of patients with ARN evaluated 14 eyes of 12 patients who received combination systemic antiviral and intravitreal foscarnet therapy and 15 eyes of 12 patients who received systemic therapy alone (level II).[29] These eyes were previously analyzed by Flaxel et al.[30] Patients were excluded if the ARN diagnosis was inconclusive or if less than 6 months of follow-up data were available. Patients in the systemic antiviral group received intravenous acyclovir 10 mg/kg 3 times daily for 2 weeks, followed by acyclovir 800 mg 5 times daily or valacyclovir 1000 mg 3 times daily. Patients treated with combination therapy received intravenous acyclovir 10 mg/kg 3 times daily or oral valacyclovir 1000 mg 3 times daily in combination with serial foscarnet injections (2.4 mg/0.1 ml) every 3 to 4 days until disease quiescence was achieved (median, 3 injections; range, 1−7 injections). Famciclovir

Table 3. Studies Reporting the Role of Laser Retinopexy to Decrease the Risk of Retinal Detachment

Author(s), Year	Level	No. of Eyes	RD Incidence	Initial Group Differences	Study Limitations
Lau et al[10] 2007	II	17 lasered 10 not lasered 27 total	35% lasered 80% not lasered	Initial VA better in laser group	Not lasered if severe media opacity or RD present
Tibbetts et al[15] 2010	II	19 lasered 39 not lasered 58 total	58% lasered 46% not lasered	Initial VA better in laser group	No comment about decision to laser
Sternberg et al[54] 1988	III	12 lasered 6 not lasered 18 total	17% lasered 67% not lasered	Initial VA, degree of retinitis better in laser group	Media opacity precluded laser in 5/6 eyes
Crapotta et al[51] 1993	III	13 eyes had laser No control	23%	No control group	Initial VA 20/60 or better in 7/13 eyes
Sims et al[34] 2009	III	15 lasered 8 not lasered 23 total	40% lasered 38% not lasered	Unknown	No comment on presenting features in groups
Meghpara et al[11] 2010	III	6 lasered 19 not lasered 25 total	0% lasered 26% not lasered	Initial VA similar	Variable follow-up, 5 patients <2 wks
Cochrane et al[2] 2012	III	11 lasered 32 not lasered 43 total	22% lasered 44% not lasered	Initial VA similar	No comment on initial disease severity

RD = retinal detachment; VA = visual acuity.

500 mg 3 times daily was used as an alternative if acyclovir was contraindicated. There was no significant difference between groups in presenting VA, but follow-up was shorter in the combination group (27 vs. 64 months). Patients receiving combination therapy were more likely to gain 2 or more lines of VA ($P = 0.01$) and showed a significant decrease in incidence of RD ($P = 0.03$). The incidence of severe vision loss to 20/200 or worse was reduced in the combination group.

Both comparative studies that assessed the role of intravitreal foscarnet found a benefit of using combination systemic and intravitreal foscarnet therapy to reduce severe vision loss or reduce the incidence of RD.[29,30,35] The mean vitreous foscarnet concentration in patients receiving intravenous induction doses (180 mg/kg/day) was 189±177 μmol/L (23.3±21.8 μg/ml).[53] Although there are no published human studies on the vitreous concentration of foscarnet after intravitreal administration, an injected dose of 2.4 mg in an adult eye with a vitreous volume of 4 ml suggests an initial vitreous concentration that is approximately 20- to 30-fold higher than after intravenous administration, which far exceeds reported IC_{50} values.

Adjunctive Treatments of Acute Retinal Necrosis

Prophylactic Laser to Prevent Retinal Detachment. Because of the high incidence of RD in ARN, some ophthalmologists have advocated prophylactic laser retinopexy to lessen this risk. Seven studies included information on prophylactic laser and were deemed sufficiently relevant to analyze in full (Table 3).

Sternberg et al[54] (level III) reviewed 18 eyes of 15 patients without RD at presentation. Retinal detachment developed in 2 of 12 eyes that received laser (17%). Four of 6 eyes that did not

Table 4. Studies Reporting Early Vitrectomy before Retinal Detachment

Author(s), Year	Level	No. of Eyes	Initial Group Characteristics	RD Incidence	Visual Outcomes
Iwahashi-Shima et al[55] 2013	II	104 eyes 48 early PPV	Similar VA at baseline	70% in observation group Final attachment in 75% of observation group and 58% of early PPV group	No difference between groups Eyes with peripheral disease fared better with observation
Hillenkamp et al[9] 2009	III	30 eyes 10 early PPV	Similar vision, time to diagnosis, and extent of necrosis	90% of observation group 40% of early PPV group	Similar between groups
Ishida et al[56] 2009	III	18 eyes 11 early PPV	More extensive retinitis in early PPV group Statistical analysis of baseline VA not provided	3/7 (43%) of observation group 3/11 (27%) of early PPV group	Statistical analysis of final vision not provided
Luo et al[57] 2012	III	37 eyes 16 early PPV	Necrosis significantly more extensive in observation group	71% of observation group 13% of early PPV group	Significantly better final vision in early PPV group

PPV = pars plana vitrectomy; RD = retinal detachment; VA = visual acuity.

receive laser developed an RD (67%). However, in 5 of these 6 eyes, the media was too opaque to allow for retinopexy. Baseline features were different between groups. More than 6 clock hours of retinitis was seen in 17% of eyes treated with laser compared with 67% that were not. Initial VA was 20/400 or better in all eyes in the laser group, but 3 of 6 eyes that did not undergo retinopexy had a VA of 3/400 or worse.

Tibbetts et al[15] (level II) reviewed 58 eyes with ARN, half of which developed RD. In eyes that underwent laser, RD developed in 58% (11/19) compared with 46% (18/39) of eyes that did not undergo laser ($P = 0.40$). There was no comment about the selection of patients for prophylactic laser versus observation. Mean VA at presentation was 20/95 in the laser group and 20/360 in the untreated group ($P = 0.003$). Visual acuity at the final follow-up visit was not different between groups.

Three retrospective comparative studies[2,10,11] found a reduced incidence of RD in patients receiving prophylactic laser, but all of these studies had limitations that confound interpretation of the results. Cochrane et al[2] (level III) reported results in a questionnaire-based study at 2 time points (initial, 6 months), but initial disease severity and reasons for laser were not reported. In the study by Meghpara et al[11] (level III), laser was applied only in patients with media clear enough to apply retinopexy. Several patients had less than a 2-week follow-up. In the study by Lau et al[10] (level II), laser retinopexy was not performed in cases with severe media opacity. Presenting VA was worse in eyes that did not have laser. One retrospective comparative study[34] (level III) found no difference in RD between eyes that did (40%) and did not (38%) receive prophylactic laser. One noncomparative, uncontrolled level III study[51] reviewed 13 eyes of 12 patients, and 23% of eyes developed RD despite prophylactic laser.

In many studies, selection bias limits the interpretation of results. For example, eyes that received prophylactic laser in many cases had clearer media with better presenting VA and less-involved retinitis than eyes that did not have laser. Therefore, on the basis of the available evidence at this time, it cannot be concluded whether prophylactic laser to prevent RD in the setting of recent ARN is of benefit.

Early Vitrectomy before Retinal Detachment. Early PPV for ARN before RD develops has been advocated for several reasons. It allows for the removal of inflammatory mediators, the removal of vitreous traction, the application of more complete laser demarcation to necrotic retina, and the placement of a long-acting tamponade to prevent subsequent RD. Four studies[9,55-57] have reviewed visual and anatomic outcomes after early PPV before RD development (Table 4).

The largest study was conducted by Iwahashi-Shima et al[55] (level II), who reviewed 104 eyes with ARN, 48 of which underwent early PPV. All patients had a minimum 12-month follow-up (median, 45 months). The decision to pursue early vitrectomy versus observation was not described. Baseline VA was not statistically significantly different between groups, and there was no difference between groups at the final follow-up visit. Final retinal attachment was achieved in 58% of eyes in the early vitrectomy group compared with 75% of eyes in the observation group.

Three retrospective comparative level III studies evaluated early PPV before the development of RD. Luo et al[57] performed early PPV on 16 of 37 eyes. In the nonvitrectomy group, RD developed in 71% of eyes and only 33% achieved final retinal attachment. In the early vitrectomy group, RD occurred in 13% of eyes. The early vitrectomy group achieved significantly better final VA. However, baseline characteristics were unbalanced because necrosis was significantly more extensive in the nonvitrectomy group ($P < 0.05$). In a study by Hillenkamp et al,[9] all 20 eyes that presented before 2002 were treated medically. All 10 eyes that presented after 2002 were treated with early PPV. Ninety percent of eyes treated medically developed RD compared with 40% of eyes that underwent early PPV ($P = 0.007$). Baseline characteristics were similar between groups. Despite the difference in the rate of RD, visual outcomes were similar. Ishida et al[56] reviewed 18 eyes of 17 patients. All 3 eyes with posterior disease developed RD after early PPV. Among eyes with midperipheral disease, all 8 treated with early PPV remained attached postoperatively, and 3 of 4 eyes that were treated medically developed RD. All eyes with peripheral disease were treated medically and remained attached. Baseline retinal involvement was more widespread in early PPV eyes. Statistical analysis of baseline and final VA was not provided.

The only level II study[55] of the 4 studies that reviewed outcomes after early PPV before RD development found no anatomic or visual benefit for early PPV. The level III studies found a possible benefit in terms of reducing the frequency of RD, but these studies were limited by unbalanced baseline characteristics,[56,57] variable follow-up time, and lack of a visual benefit.[9,56] Therefore, on the basis of the available evidence at this time, it cannot be concluded whether vitrectomy to prevent RD in the setting of recent ARN is of benefit.

Conclusions

Although it is an uncommon disease, ARN can be associated with substantial ocular morbidity. The rarity of ARN, lack of validated outcome measures, and its variable course have made it impracticable to attain level I evidence to guide best clinical practice. There is level II and III evidence supporting the therapeutic effectiveness of intravenous or oral acyclovir for the initial treatment of ARN and prevention of fellow eye involvement. Plasma drug levels of acyclovir can be achieved using oral valacyclovir dosed at 2000 mg 4 times daily that are comparable to intravenous acyclovir dosed at 10 mg/kg 3 times daily. These results lend support to the practice of administering high doses of oral valacyclovir as induction therapy on an outpatient basis, which may lead to substantial savings, particularly when considering the costs of hospitalization for intravenous antivirals or home nursing for intravenous medications. Doses of valacyclovir less than 2000 mg 4 times daily by mouth have been used in the studies listed above[16,17,52] and have had favorable outcomes as well.

Polymerase chain reaction testing of aqueous and vitreous humor reliably confirms cases of suspected ARN with a low overall rate of reported adverse events. Aqueous and vitreous specimens are sensitive and specific, but aqueous specimens may be safer. Aqueous testing should be

considered in cases of suspected ARN to aid in confirming the diagnosis or ruling out other masquerading diseases. In patients with suspected ARN, treatment should not be delayed while awaiting results of PCR testing.

There is a strong scientific rationale to support the adjunctive use of intravitreal foscarnet in the early treatment of ARN to attain immediate therapeutic vitreous drug levels and inhibition of viral replication. The collective body of clinical evidence also suggests a beneficial role of intravitreal foscarnet in conjunction with systemic antiviral therapy for reducing the risk of severe vision loss and incidence of RD. Furthermore, the combination of intravitreal foscarnet and systemic acyclovir may have greater efficacy against resistant herpes virus strains. However, intravitreal foscarnet should never be used without systemic antiviral therapy because it will not reduce the risk of fellow eye involvement. The benefit of other procedures such as early PPV or prophylactic laser retinopexy remains unproven.

Despite the absence of level I data, the body of evidence supports that the majority of cases of ARN (those without central nervous system involvement) can be treated on an outpatient basis with induction oral valacyclovir (6000–8000 mg daily) for 7 to 10 days. If available, early injection of intravitreal foscarnet 2.4 mg should be considered to hasten viral inactivity and limit disease extent. Diagnostic aqueous PCR testing should be performed when there is an unclear presentation or inadequate response to treatment, but it should not delay initiation of therapy. After induction therapy, longer-term maintenance therapy (typically 1000 mg valacyclovir daily) for 6 months or more is common.

Future Research

Future studies should compare oral versus intravenous antiviral therapy in the initial management of ARN. In addition, studies should compare systemic antiviral therapy alone versus systemic with adjunctive intravitreal antiviral treatment. Prospective, randomized, controlled, double-masked studies are the gold standard for determining treatment effect. However, these studies are difficult in the setting of ARN because of its rarity, and therefore properly conducted retrospective studies are more feasible. Multicenter studies will likely be necessary to generate an adequate sample size. Detailed analysis of intravitreal drug levels of acyclovir after intravenous acyclovir and oral valacyclovir may provide useful information about drug penetration and comparative therapeutic efficacy.

One limitation of the studies in the literature is the lack of uniform reporting of outcome measures. Treatment success may be defined by several modalities, including time to initial and complete regression of retinitis, visual and anatomic outcomes, and contralateral eye involvement. A clear description of the severity of disease is necessary, including VA, extent and location of retinitis (preferably using fundus photography), and degree of intraocular inflammation. Subsequent studies should focus on standardized definitions of outcomes to better assess responses and to allow for improved cross-trial comparison.

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Abbreviations and Acronyms:
ARN = acute retinal necrosis; **AUC** = area under the curve; **CPT** = Current Procedural Terminology; **HSV** = herpes simplex virus; **IC_{50}** = 50% inhibitory concentration; **PCR** = polymerase chain reaction; **PPV** = pars plana vitrectomy; **RD** = retinal detachment; **VA** = visual acuity; **VZV** = varicella zoster virus.

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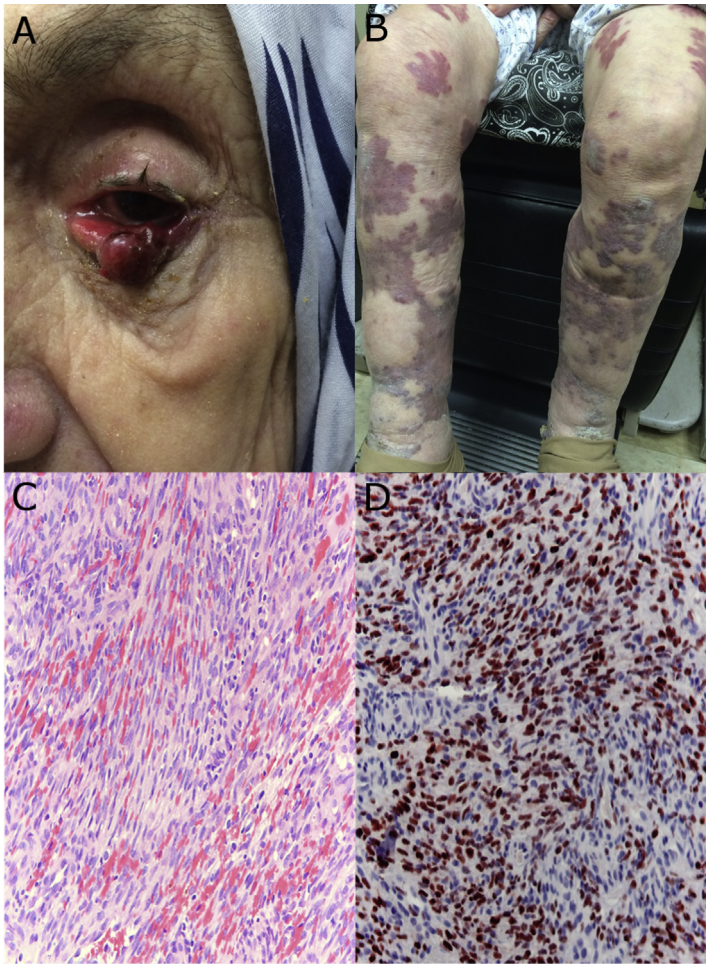
Pictures & Perspectives



Eyelid Kaposi's Sarcoma in an Immunocompetent Woman

A 94-year-old immunocompetent woman presented with a 2-month history of an enlarging, painless, violaceous, nodular lesion on the left lower eyelid with mechanical ectropion (Fig 1**A**). She had multiple, expanding, well-demarcated, violaceous patches, and thin plaques on her extremities, which appeared a few months before the lid lesion (Fig 1**B**). Incisional biopsy of the lid mass showed fascicles of monomorphic spindle cells with slit-like vascular channels containing erythrocytes (Fig 1**C**). Immunohistochemistry revealed strong immunoreactivity for human herpes virus type 8 latent nuclear antigen-1 (HHV8 LNA-1) antibody confined to the nucleus confirming Kaposi's sarcoma (Fig 1**D**).

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