Treatment of Acute Retinal Necrosis

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Objectives: To compare outcomes from patients with acute retinal necrosis (ARN) treated in the acyclovir-only era with those treated in the era of newer antiviral therapies, identify variables affecting outcomes in ARN, and evaluate strategies for fellow eye prophylaxis.

Design: Multicenter, nonrandomized, retrospective, interventional series.

Participants: A cohort of 58 patients diagnosed with ARN by a retina specialist at 1 of 4 referral centers between 1981 and 2008. The cohort was divided into 2 subgroups: patients treated during the acyclovir-only era (n = 36) and patients treated during the current era of newer antiviral medications (n = 22).

Intervention: Intravenous, oral, or intravitreal antiviral medications, including acyclovir, valacyclovir, famciclovir, valganciclovir, ganciclovir, and foscarnet; prophylactic laser retinopexy; aspirin; oral steroids.

Main Outcome Measures: Visual acuity, retinal detachment, and fellow eye involvement.

Results: A wide range and combination of antiviral agents are currently used for initial and long-term treatment of ARN. Outcomes from the newer antivirals era were similar to those achieved during the acyclovir-only era. In both groups, the incidence of 20/200 or worse visual acuity was 24% per person-year ($P = 0.91$). The prevalence of retinal detachment was approximately 50% in each group ($P = 0.59$). No variables, including prophylactic laser retinopexy, were associated with risk of retinal detachment. Two patients (3.4%) developed ARN in the initially unaffected eye.

Conclusions: Current treatment trends vary widely, including single agents or combinations of oral, intravenous, and intravitreal agents. Differing strategies did not affect outcomes. The final visual acuity in ARN was generally poor. Retinal detachment was common and could neither be predicted nor prevented. Development of ARN in the unaffected fellow eye occurred rarely. Long-term oral antiviral treatment strategies varied with unclear relative efficacy.

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Acute retinal necrosis (ARN) syndrome is an infectious retinitis caused by members of the herpes virus family (Fig 1).[1,2] It is defined by the American Uveitis Society by its clinical characteristics and disease course, not by the causative agent or patient immune status.[3] Diagnostic criteria include (1) one or more discrete foci of peripheral retinal necrosis, (2) circumferential spread, (3) occlusive arteriolar retinopathy, (4) a prominent vitreous or anterior chamber inflammatory reaction, and (5) rapid disease progression in the absence of therapy.

Acyclovir has been used to treat ARN for more than 2 decades.[4] In 1991, Palay and colleagues[5] reported that treatment of ARN with intravenous and then oral acyclovir decreased the risk of fellow eye involvement. They retrospectively compared patients treated with and without acyclovir; 12.9% of patients developed fellow eye involvement during a median follow-up of 12 months, compared with a 69.6% rate in historical untreated controls. The risk of fellow eye involvement was greatest in the first 14 weeks after diagnosis. The authors recommended oral acyclovir (800 mg 5 times daily) for 14 weeks after initial treatment with intravenously administered acyclovir (500 mg/m^2 intravenously administered 3 times daily) for 7 to 10 days.

Currently, some clinicians are initiating treatment for ARN with newer antiviral agents including oral famciclovir (Famvir; Novartis Pharmaceuticals, Basel, Switzerland) and valacyclovir (Valtrex; GlaxoSmithKline, Research Triangle Park, NC), which have greater bioavailability and central nervous system penetration.[6–12] These agents were approved for use by the U.S. Food and Drug Administration in 1994 and 1995, respectively, and have been used for both initial and long-term treatment for ARN.[13,14] In addition, intravitreal injections of foscarnet (1.2–2.4 mg per 0.1 ml) and ganciclovir (200–2000 μg per 0.1 ml) have been used for adjunctive therapy.[15,16] Despite these advances, the optimal antiviral choice, route(s) of administration and course for initial treatment, and long-term prophylaxis have not been defined. Questions also remain regarding the use of prophylactic laser retinopexy, antiplatelet agents, and steroids.[17–21]

Given the rare occurrence of ARN, most studies have been hampered by a modest number of cases, sometimes yielding conflicting conclusions. With this in mind, we collected a large database of patients from 4 institutions spanning over 25 years. In this retrospective cohort study, our aims were to identify variables affecting outcomes in ARN, compare current treatment strategies with past eras, and evaluate fellow eye prophylaxis.

Patients and Methods

The authors retrospectively reviewed records of patients with ARN at 4 ophthalmic referral centers: Ophthalmic Consultants of Boston, Boston, Massachusetts; Massachusetts Eye and Ear Infirmary, Boston, Massachusetts; Wills Eye Institute, Philadelphia, Pennsyl-

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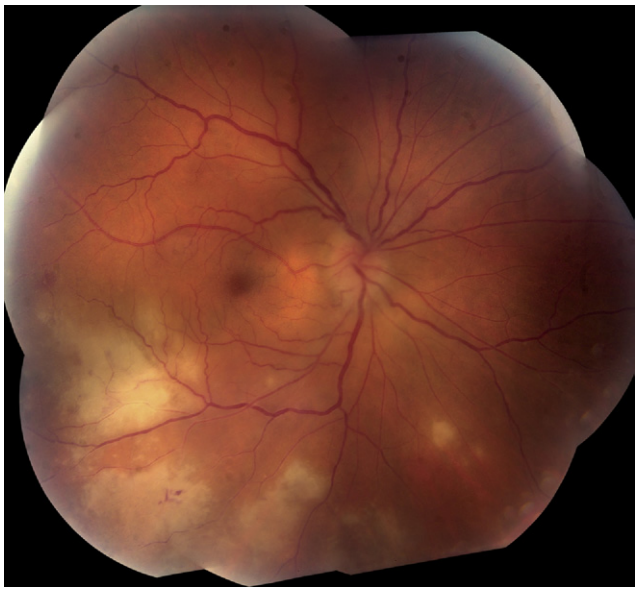

Figure 1. Color fundus montage of ARN revealing vitritis, vasculitis, retinitis, and optic nerve involvement. ARN = acute retinal necrosis.

vania; and Tufts New England Medical Center, Boston, Massachusetts. Charts of patients with ARN were located using International Classification of Diseases, 9th Revision codes. A total of 58 unilateral ARN cases with a minimum follow-up time of 6 months were identified between 1981 and 2008. The diagnosis of ARN was established using criteria established by the American Uveitis Society. Before the publication of the American Uveitis Society guidelines in 1994, inclusion criteria consisted of clinical criteria, including a rapidly progressive necrotizing retinitis, and prominent intraocular inflammation, including vitritis and vasculitis. Exclusion criteria included follow-up less than 6 months and bilateral ARN before initiation of treatment.

Medical records were reviewed to collect the following data: date, age, sex, medical history, ocular history, visual acuity, presence of vitritis, optic nerve edema or pallor, retinal detachment, prophylactic laser retinopexy, surgical repair of retinal detachment, antiviral therapy (type, dose, and duration), aspirin use, oral corticosteroid use, presence of fellow eye involvement, and duration of follow-up. Three researchers (MDT, CPS, JIM) were responsible for data extraction and tabulation. Institutional review board approval was obtained from each participating institution.

Statistical analyses were performed using Excel (Microsoft, Redmond, WA) and Stata 9 (StataCorp, College Station, TX) with visual acuity data converted to the logarithm of the minimum angle of resolution (logMAR). The following conversion to logMAR was used for vision worse than 20/400: counting fingers = 1.6, hand movements = 2.0, light perception = 2.5, and no light perception = 3.0.[22–24] Light perception has assigned a logMAR value of 2.3 ("intact light perception," Retina paper), 2.5 (Arroyo), and 2.7 ("defect light perception," Retina paper); we assigned a logMAR value of 2.5 for light perception because it was the median value. Paired and unpaired Student *t* tests were used to compare mean logMAR vision, where appropriate. Because of variable follow-up times, an interval comparison at 6 months was performed for visual acuity. Furthermore, relevant incidence rates were reported, calculated by dividing the number of events by person-time.[25] A 2-sample test of proportion was used to compare proportions between groups.

Logistic regression analysis examined risk factors for retinal detachment and fellow eye involvement, whereas linear regression analysis examined risk factors for final visual acuity. Each variable was first evaluated using univariate regression. *P* values of less than 0.10 were included in the multivariate regression. Variables tested included the year of diagnosis, age, sex, immunocompromised state, antiviral agent, route of antiviral administration, duration of oral antiviral treatment, number of days between symptom onset and antiviral initiation, initial vision in the affected eye, initial vision in the fellow eye, optic nerve involvement, aspirin use, oral corticosteroid use, prophylactic laser retinopexy, and duration of follow-up.

Kaplan–Meier survival analysis was performed using Stata 9. A log-rank test was used to compare variables. For the visual acuity analysis, a failure was defined as 20/200 vision or worse. For cases never achieving better than 20/200 vision from presentation, a failure time of 0.1 years was used so that these cases could be included in the analysis and graph. For the retinal detachment analysis, a failure was defined as the development of a retinal detachment.

Results

A total of 58 patients with unilateral ARN were identified. The acyclovir-only era subgroup contained 36 cases, whereas the newer antiviral era subgroup contained 22 cases (Table 1). The total cohort was divided into 2 subgroups to compare past and current treatment modalities. The first subgroup, herein called the "acyclovir-only era" subgroup, comprised patients treated during a time when acyclovir was the only available antiviral treatment. The second cohort, herein called the "newer antiviral era" subgroup, comprised patients treated during the era of new antivirals such as valacyclovir and famciclovir. Although these medications were Food and Drug Administration approved in 1995 and 1994, respectively, they were not used in any of our cases until after 1998. Moreover, the first use of famciclovir to treat ARN was reported in 1997.[7] Thus, the acyclovir-only subgroup contained cases from 1981 to 1997, whereas the newer antiviral era subgroup contained cases from 1998 to 2008.

The patients during the acyclovir-only era were treated initially with intravenous acyclovir (500 mg/m^2 3 times per day) for a period of 7 to 10 days. Half of the patients (18/36) were further treated with oral acyclovir 800 mg 5 times per day for at least 6 weeks, whereas the other half were not treated with oral acyclovir. The decision of whether or not to treat with oral acyclovir was dependent on the particular practice pattern of the treating physician and was not influenced by the severity of the disease.

Table 1. Summary of Patients with Acute Retinal Necrosis

	Total	Acyclovir-only Era	Newer Antiviral Era	P Value
No. of patients with unilateral ARN	58	36	22	
Average age, yrs	48	44	54	0.042
Female	55% (32)	56% (20)	55% (12)	0.940
Male	45% (26)	44% (16)	45% (10)	
Mean duration of follow-up (mos)	34.5	37.8	29.1	0.310
Median duration of follow-up (mos)	23.9	24.0	21.5	
Follow-up >1 yr	81% (47)	89% (32)	65% (15)	0.051
Immunosuppressed*	19% (11)	17% (6)	23% (5)	0.568

ARN = acute retinal necrosis.
*Immunosuppression by iatrogenic cause or systemic disease.

The "newer antiviral era" patients were all treated with systemic antiviral agents, including intravenous acyclovir, intravitreal antiviral injections, oral antiviral therapy, or some combination thereof. Six different treatment regimens were used for initial treatment (Table 2). Systemic corticosteroids (initial dose of 30–80 mg daily) were initiated in 77% of patients (17/22) and typically tapered over 2 to 6 weeks. All eyes received topical steroids (prednisolone acetate 1% every 1–6 hours) during the initial treatment period. Fifty-nine percent of patients (12/22) in the newer antiviral group underwent pars plana vitrectomy for diagnostic sampling, vitreous hemorrhage, or retinal detachment. Of eyes in the newer antiviral group, 41% (9/22) were given a viral diagnosis either by polymerase chain reaction or by correlation with recent skin infection or encephalitis; 44% (4/9) were herpes simplex virus and 56% (5/9) were varicella zoster virus.

Visual Acuity

Visual acuity in eyes affected with ARN significantly worsened in both the acyclovir-only era patients and the newer antiviral era patients. Kaplan–Meier analysis was used to assess the progression to 20/200 or worse visual acuity (n = 58). Half of all patients had 20/200 or worse vision by 3 months, and 75% had 20/200 or worse vision by 5 years (Fig 2). Kaplan–Meier analysis was stratified by the acyclovir-only era and the newer antiviral era. There was no difference in risk of 20/200 or worse visual acuity in either era (P = 0.51, log-rank test) (Fig 3). The rate of visual loss to 20/200 or worse was nearly identical in both eras, measuring 24% per person-year (P = 0.91).

Because of variable follow-up between cases, an interval analysis was performed at 6 months to compare visual acuity between the newer antiviral era and the acyclovir-only era. The mean logMAR vision at 6 months was significantly better in the newer antiviral era compared with the acyclovir-only era (1.24 [20/345]) vs. 1.74 [20/1093], P = 0.042, difference of −0.50, 95% confidence interval [CI], −0.98 to −0.020, unpaired Student t test, unequal variance).

Visual acuity worsened in both treatment eras at 6 months. Six-month visual acuity was available for all 22 patients in the newer antiviral era. The mean initial logMAR vision was 0.946 (20/177), decreasing to 1.24 (20/345) at 6 months (P = 0.10, paired t test). Six-month visual acuity was available for 25 patients in the acyclovir-only era. The mean initial logMAR vision for these 25 patients was 1.24 (20/351), decreasing to 1.74 (20/1093) at 6 months (P = 0.0015, paired t test). Although patients in the newer antiviral era were diagnosed with ARN at better initial visual acuities than cases during the acyclovir-only era, this difference was not statistically significant (0.946 vs. 1.14, n = 58, P = 0.37, unpaired Student t test).

Risk factors for worse final visual acuity include initial visual acuity (odds ratio [OR] = 1.57, P = 0.002) and retinal detachment (OR = 2.13, P = 0.001, multivariate linear regression). Earlier year of diagnosis was associated with worse final visual acuity, although this was of borderline statistical significance in the regression model (OR = 0.97, P = 0.064). Aspirin use was associated with better final visual acuity in univariate linear regression (OR = 0.56, P = 0.055) but became nonsignificant in the multivariate model. Initial intravenous antiviral treatment (OR = 1.23, P = 0.64), initial intravitreal antiviral treatment (OR = 0.88, P = 0.73), days between symptoms and treatment (OR = 1.01, P = 0.71), duration of oral antiviral treatment (OR = 1.00, P = 0.72), oral steroid use (OR = 0.98, P = 0.94), prophylactic laser therapy (OR = 0.85, P = 0.55), optic nerve involvement (OR = 1.28, P =

Table 2. Initial Antiviral Treatment in Newer Antiviral Era

	n = 22	%
IV acyclovir only (range 140–1000 mg 3× daily)	9	41%
Oral antiviral medication only (acyclovir 800 mg 5× daily or valacyclovir 1–2 g 3× daily)	3	14%
IV acyclovir and intravitreal injection (foscarnet or ganciclovir)*	5	23%
Oral antiviral medication (valacyclovir or famciclovir) followed by IV acyclovir	2	9%
Oral medication and intravitreal injection (foscarnet or ganciclovir)*	2	9%
IV acyclovir, oral medication, and intravitreal injection	1	5%
Total who received IV acyclovir	17	77%
Intravitreal injections alone or with other therapy	8	36%

IV = intravenous.
*Foscarnet dose range 1.2–2.4 mg in 0.1 ml, ganciclovir dose range 200–400 μg in 0.1 mL.

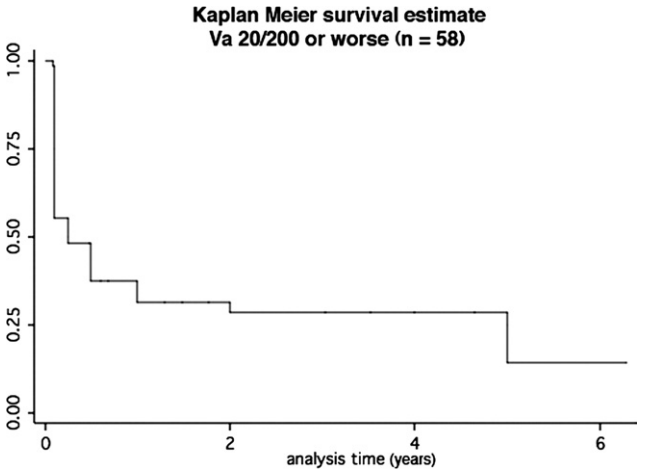

Figure 2. Kaplan–Meier survival estimate of the proportion of cases with ≤20/200 visual acuity.

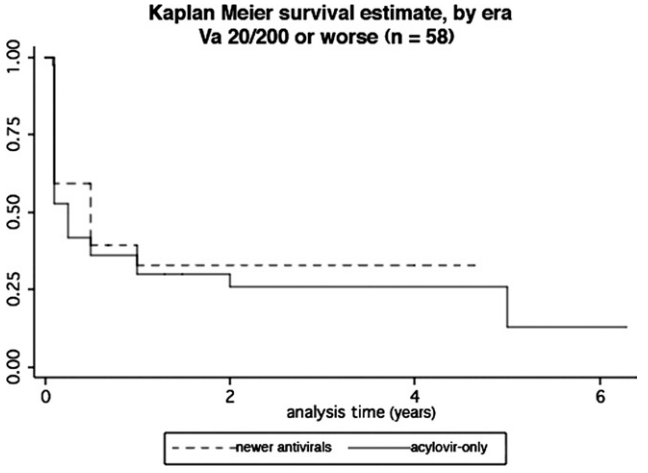

Figure 3. Kaplan–Meier survival estimate of the proportion of cases with ≤20/200 visual acuity, stratified by era. There is no difference in risk of ≤20/200 visual acuity in either the current antiviral era or the acyclovir-only era (P = 0.51, log-rank test).

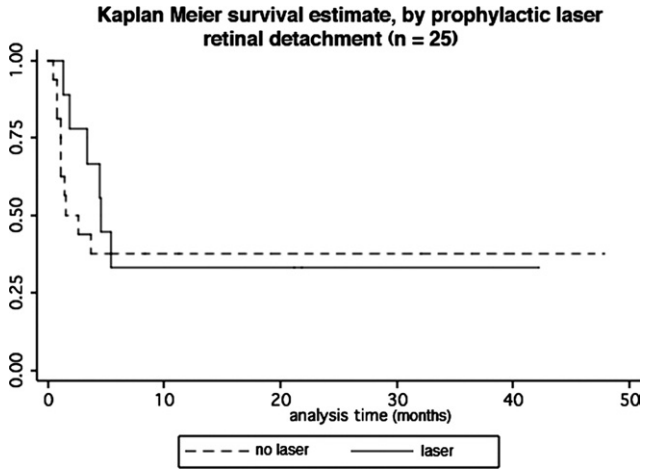

Figure 4. Kaplan–Meier survival estimate of the proportion of cases developing retinal detachment, stratified by prophylactic laser retinopexy. There is no difference in risk of retinal detachment based on prophylactic laser ($P = 0.59$, log-rank test).

0.34), and immunocompromised state (OR = 1.01, $P = 0.97$) did not affect final visual acuity.

Retinal Detachment

Half (29/58, 50%) of patients developed retinal detachment with a similar prevalence between the newer antiviral era and acyclovir-only eras (55% vs. 47%, respectively, $P = 0.59$). Because of variable follow-up, we calculated retinal detachment incidence rates. The rate for the newer antiviral era was 23% per person-year, compared with 15% per person-year in the acyclovir-only era ($P = 0.22$). The overall rate was 17% per person-year. One caveat is that the shorter follow-up for the newer antiviral treatment group may skew these incidence rates. All detachments occurred within 6 months, our minimum follow-up time; there were no retinal detachments reported beyond 5.4 months. Retinal detachment occurred a median of 53 days after initial presentation (mean 74 days with a range of 28–165 days) in 16 patients with known dates of detachment.

The entire cohort of 58 unilateral ARN patients was analyzed to determine risk factors for retinal detachment. No variables predicted risk of retinal detachment, including prophylactic laser retinopexy (OR = 1.60; $P = 0.40$; 95% CI, 0.53–4.85), initial intravenous antiviral treatment (OR = 2.16, $P = 0.40$), initial intravitreal antiviral treatment (OR = 1.00, $P = 1.00$), days from symptoms onset to treatment (OR = 1.01, $P = 0.91$), duration of oral antiviral treatment (OR = 1.03, $P = 0.287$), initial visual acuity (OR = 0.97, $P = 0.92$), oral steroid use (OR = 1.16, $P = 0.79$), and aspirin use (OR = 1.00, $P = 1.00$).

Prophylactic laser retinopexy did not affect the risk of retinal detachment. Prophylactic laser retinopexy was used in 33% of patients (19/58) during their treatment course, at the judgment of the treating physician. Retinal detachment occurred in 58% of patients (11/19) who received prophylactic laser treatment and 46% of patients (18/39) who did not receive prophylactic laser treatment ($P = 0.40$). The difference between prevalence rates was 12% with a 95% CI of −15% to 39%. The incidence of retinal detachment was 19.3% per person-year among those receiving prophylactic laser treatment, and 16.4% per person-year among those who did not receive prophylactic laser treatment ($P = 0.64$).

Kaplan–Meier analysis was used to assess the risk of developing retinal detachment. Time data were available for 25 patients, 16 of whom developed retinal detachment. Half of these patients developed a retinal detachment by 3.7 months. Kaplan–Meier analysis was stratified by cases receiving and not receiving prophylactic laser retinopexy; there was no difference in the risk of retinal detachment ($P = 0.59$, log-rank test) (Fig 4).

Prophylactic laser did not affect visual acuity outcomes. Patients treated with prophylactic laser retinopexy had significantly better visual acuity at presentation and time of treatment. The average initial vision was 20/95 in the prophylactic laser treatment group compared with 20/360 in the untreated group ($P = 0.003$). Laser retinopexy did not affect the risk of visual acuity decreasing to 20/200 or worse. Final visual acuity was worse than 20/200 in 72% of those not receiving laser retinopexy and 63% of those receiving laser retinopexy ($P = 0.50$, 2-sample test of proportion). Because of variable follow-up, incidence rates were calculated. The incidence rate of 20/200 or worse visual acuity in the prophylactic laser retinopexy group was 21% per person-year, compared with 25% per person-year among those who did not receive laser retinopexy ($P = 0.53$).

Fellow Eye Prophylaxis

In the newer antiviral era subgroup, treating ophthalmologists used 4 different oral antiviral medications with a wide range of dosages and durations for long-term ARN treatment and fellow eye prophylaxis (Table 3). Valacyclovir was the most common antiviral prescribed (12/22, 55%). Duration of long-term antiviral therapy varied widely ranging from 1.5 to 75.7 months, with a median of 9.6 months and mean of 19.1 months. Oral antiviral regimens were tapered in 52% of cases (9/22) during the follow-up course. Of patients at the last recorded visit, 48% (10/22) were still taking antiviral medication, 33% (7/22) had antiviral medication discontinued by ordering provider, and 19% (4/22) were lost to follow-up.

Fellow Eye Involvement

Two of 58 patients (3.4%) developed ARN in the unaffected eye after initial antiviral treatment. The first patient was treated initially with intravenously administered acyclovir and then prescribed extended therapy with valacyclovir. This patient missed several days of medication (valacyclovir 500 mg twice daily) before the onset of symptoms in the fellow eye at 37 months. After diagnosis of the fellow eye involvement, the patient was treated with intravenous acyclovir (800 mg every 8 hours for 14 days) and then maintained on oral antiviral treatment with famciclovir (Famvir) 500 mg twice daily with excellent vision (20/16) at final follow-up 29 months later; no retinal detachment occurred. The second patient was treated initially with oral valacyclovir (2000

Table 3. Long-term Oral Antiviral Treatment/Prophylaxis Regimens in Newer Antiviral Era

Initial Oral Antiviral Medication	N = 22	%	Mean (mos)	Median (mos)
Valacyclovir (Valtrex; GlaxoSmithKline, Research Triangle Park, NC) (1000 mg daily to 1000 mg 3× daily)	12	57%	26.6	16.2
Acyclovir (400–800 mg 5× daily)	5	23%	3.3	3.5
Famciclovir (Famvir; Novartis Pharmaceuticals, Basel, Switzerland) (250–500 mg 2× daily)	3	14%	17.4	21.8
Valganciclovir (Valcyte; Roche Laboratories, Indianapolis, IN) (450–900 mg 2× daily)	2	9%	6.0	6.0

mg 3 times daily), which was then tapered over 4 months to a lower dose (valacyclovir 500 mg 3 times daily). Vision in the fellow eye decreased to 20/200 at time of involvement 8 months after initial presentation. The dose of valacyclovir was increased to 1000 mg 3 times with disease control and vision returning to 20/32.

Logistic regression analysis of the 58 patients with unilateral ARN did not associate any variables with risk of fellow eye involvement, including year (OR = 1.23, $P = 0.22$), age (OR = 0.98, $P = 0.56$), initial visual acuity in the affected eye (OR = 2.30, $P = 0.35$), initial intravenous antiviral treatment (OR = 0.10, $P = 0.12$), initial oral antiviral (OR = 6.0, $P = 0.22$), oral steroid use (OR = 0.56, $P = 0.68$), duration of oral treatment (1.04, $P = 0.19$), duration of follow-up (OR = 1.00, $P = 0.90$), or days between symptoms and antiviral treatment (OR = 0.96, $P = 0.67$). A 2-sample test of proportion showed a borderline higher rate of fellow eye involvement during the newer antiviral era compared with the acyclovir-only era ($P = 0.066$).

Discussion

The traditional treatment paradigm for ARN since the 1980s has been induction therapy with intravenous acyclovir (500 mg/m^2 3 times per day) for 7 to 10 days followed by oral antiviral medications for approximately 14 weeks.[5] Newer antiviral treatment strategies, including intravitreal and oral regimens, have emerged over the past decade to challenge the traditional acyclovir-only paradigm. Agents such as valacyclovir afford excellent bioavailability and intraocular penetration with more convenient dosing schedules than oral acyclovir.[11,26]

Our analysis of current treatment practices at 4 tertiary eye care centers identified no single treatment strategy as the standard of care for ARN (Table 2). Initial treatment strategies included intravenous acyclovir, intravenous acyclovir with intravitreal antivirals, oral antiviral with intravitreal antivirals, and oral antivirals alone. The majority underwent induction with intravenous acyclovir (17/22, 77%). More than one third of patients received intravitreal foscarnet or ganciclovir (8/22, 36%), with all injections performed since 2005. A small percentage of patients (3/22, 14%) were treated with oral antiviral therapy alone (2 with valacyclovir, 1 with acyclovir). Initial antiviral strategy did not affect final visual outcome, suggesting that the treating ophthalmologist may use his or her own judgment on the basis of available resources.

Our study also revealed significant variation in long-term oral antiviral treatment strategies prescribed to prevent recurrence and fellow eye involvement (Table 3). Treatment duration varied greatly, ranging from 1.5 to 75.7 months. Most patients were maintained on valacyclovir (1000 mg daily to 1000 mg 3 times daily). Other regimens included acyclovir (400–800 mg 5 times daily), famciclovir (250–500 mg twice daily), and valganciclovir (450–900 mg twice daily). The ideal duration and relative efficacy of these long-term oral antiviral regimens remain unclear.

The visual outcome after ARN was generally poor[1,2,20] (Fig 2) and worsened from presentation in both the acyclovir-only and newer antiviral eras. There was no difference in visual acuity outcome between the 2 eras (Fig 3), leading to the sobering conclusion that outcomes have not improved since the approval of acyclovir in 1982.[13] Neither aspirin, thought to treat platelet hyperaggregation, nor oral steroids, often prescribed to treat vitritis, affected visual outcomes. Poorer initial visual acuity and the development of a retinal detachment each predicted worse final visual acuity. One promising finding is that initial visual acuity was better during the newer antiviral era, suggesting more timely clinical recognition and diagnosis of ARN. Further, the development of polymerase chain reaction-based detection methods from anterior chamber taps permits a definitive viral diagnosis and may hasten earlier antiviral therapy.[27] The lack of difference between the 2 eras suggests that ARN can be managed by a myriad of outpatient treatment strategies with similar visual outcomes as intravenous acyclovir. Of note, however, is that our comparison of the newer antiviral era and acyclovir-only era is tempered by the retrospective design of the study. Factors other than the prescribed antivirals, such as diagnostic criteria and protocols for determining vision, may have been inconsistent between eras.

No variables predicted or prevented the risk of retinal detachment. Prevalence rates were similar in both the newer antiviral and acyclovir-only eras. As in other studies,[20,28] 50% of patients developed retinal detachment. The median time of retinal detachment was 53 days after presentation, ranging from 28 to 165 days.

There is considerable debate regarding the benefit of prophylactic laser retinopexy; some studies claim a benefit[18,20,29] and others suggest that retinal detachment rates remain unchanged.[21] In our report, prophylactic laser retinopexy affected neither the risk of retinal detachment (Fig 4) nor the visual acuity outcomes. Patients receiving prophylactic laser must have limited vitritis to allow adequate visualization of the retina. To strengthen our finding, we report that patients receiving prophylactic laser treatment had significantly *better* initial visual acuity—and likely less vitritis—than those who did not receive laser treatment. Thus, because vitritis can predispose one to retinal tears, patients selected for prophylactic laser should be at significantly *lower* risk of rhegmatogenous retinal detachment. Our finding argues against the utility of prophylactic laser retinopexy. However, despite this selection bias and our relatively large sample of 58 cases, our results must be tempered by the wide CIs. Although prophylactic laser retinopexy *increased* the odds of retinal detachment by logistic regression (OR = 1.6), the 95% CI was 0.53 to 4.85. Similarly, the prevalence rate of retinal detachment was *higher* in those receiving prophylactic laser treatments (58%) versus those who did not receive prophylactic laser treatment (46%), but a 2-sample test of proportion revealed a wide 95% CI around the difference of 12% (−15% to 39%). Therefore, we cannot exclude the possibility that prophylactic laser may provide a small benefit if evaluated in a larger cohort.

The rate of fellow eye involvement in unilateral ARN decreased dramatically after the advent of acyclovir. Palay et al[5] reported that acyclovir decreased the risk of fellow eye involvement from 75.3% to 35.1% at 2 years after initial onset, putatively by suppressing viral spread during the first few weeks of therapy. A more recent study reported a fellow eye involvement rate of 13.6%,[19] with a mean follow-up of 4 years

(range of 1.0–12.2 years). We report a very low rate of fellow eye involvement (3.4%) with a median follow-up of 24 months. It remains unclear why our rate is lower than that that of other published reports, particularly our rate during the acyclovir-only era (0/36 cases). Our low rate may be due to selection bias, because we excluded patients with bilateral ARN and potentially selected those subjects with timely diagnosis and initiation of treatment. Alternatively, our low rate could be due to chance. Fellow eye involvement can occur decades later, so our final rate remains to be determined.[30,31]

We did not identify any risk factors for fellow eye involvement. One patient, initially treated with intravenous acyclovir, developed fellow eye involvement at 37 months after running out of oral valacyclovir, suggesting adequate viral suppression by valacyclovir. The other patient, initially treated with high-dose oral valacyclovir, developed fellow eye involvement on a lower dose 8 months later. Both patients responded well to more aggressive antiviral therapies.

Although our study has offered additional data on the treatment of ARN, we cannot definitively recommend a superior treatment strategy. Normally, such a recommendation would require a randomized control trial, but this remains infeasible with a disease as rare as ARN. To illustrate, it would require 268 patients with ARN to detect a 50% versus 30% difference in retinal detachment rates with and without prophylactic laser retinopexy (power 90%, alpha 0.05, 2-sided test). Detecting a 3.4% rate of fellow eye involvement versus a 6.8% rate would require 1872 patients with unilateral ARN. With 100% enrollment, it would take our 4 institutions more than 500 years to amass this sample. As such, we recommend that future studies, which we expect to be retrospective in nature, report incidence rates of important outcome measures including visual acuity worse than 20/200 and retinal detachment with and without prophylactic laser retinopexy. These incidence rates can be combined ultimately in a meta-analysis. Further, in the setting of variable follow-up, we encourage interval analyses and Kaplan–Meier estimates, rather than final visual acuity outcomes.[25]

In conclusion, we reported a wide range of current treatment strategies for ARN, all associated with similar outcomes. There were no differences in outcome between the newer antiviral era and the acyclovir-only era. Our study confirmed that visual outcomes in patients with ARN were generally poor, and our results did not support one optimal strategy. Initial visual acuity and development of a retinal detachment predicted visual prognosis. Prophylactic laser retinopexy did not prevent retinal detachment in ARN. Perhaps several different strategies yield similar results; identifying more subtle differences in outcome will require an even larger cohort or meta-analysis of this rare disease. Our rate of fellow eye involvement was low. We did not identify any risk factors for fellow eye involvement, an analysis limited by the small number of affected cases.

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