

A COMPARATIVE STUDY BETWEEN ORAL VS COMBINED ANTIVIRAL IN ACUTE RETINAL NECROSIS (ARN)

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ARN: Acute retinal necrosis, AIDS: Acquired immuno deficiency syndrome, CMV: Cytomegalo virus, FFA: Fundus fluorescein angiography, HIV: Human immuno virus, HSV: Herpes simplex virus, LogMar: Logarithm of the minimum angle of resolution, OCT: Optical coherence tomography, PCR: Polymerase chain reaction, USG-B scan: Ultra sonography B scan, VZV: Varicella zoster.

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Abstract

Background: Acute retinal necrosis (ARN) is a distinct ocular inflammatory condition with a constellation of clinical features and vision-threatening complications. The American uveitis society recommended diagnostic criteria for all clinical and laboratory studies in acute retinal necrosis. The main etiological factor for acute retinal necrosis is the herpes family virus. The aim is to compare the treatment outcomes and long-term complications in ARN patients treated with only oral and combined antiviral therapy. **Materials and Methods:** All patients diagnosed with acute retinal necrosis were given oral or combined antiviral therapy. In Oral antiviral therapy (Group1), T.Valacyclovir 1000mg TDS/day was given for 8 to 12 weeks. Combined antiviral therapy (Group 2) includes a combination of oral antiviral, intravitreal antiviral, intravenous antiviral, and intravitreal antiviral. **Result:** 21 of 18 patients were studied, 11 were males, and seven were females. Bilateral involvement was seen in 3 patients. Fifteen eyes were given oral valacyclovir as sole antiviral (Group 1), and six were given combined antiviral therapy (Group 2). In oral therapy, four eyes (26.67%) out of 15 eyes progressed to retinal detachment, and three eyes out of 6 (50%) progressed to retinal detachment in a combined therapy group. A statistically significant (P=0.033) improvement in visual acuity between initial and final vision in oral therapy. A statistically significant (P=0.02) exists between mean initial visual acuity between oral and combined therapy. Mean initial visual acuity was better in an oral group than combined group. **Conclusion:** Acute retinal necrosis is a rare but potentially blinding disease. Prompt diagnosis and a good therapeutic approach lead to better visual recovery. Vision-threatening complications like retinal detachment can be prevented by prompt treatment. Primary treatment with oral antiviral for indolent ARN is an effective alternative to combined therapy as the latter is invasive and requires hospitalization.

INTRODUCTION

Acute retinal necrosis (ARN) is a distinct ocular inflammatory condition with a constellation of clinical features and vision-threatening complications. Acute retinal necrosis is a visually devastating disease. Prompt diagnosis and a good therapeutic approach are a must for better visual recovery. Akira Urayama et al. [1], in the year 1971, reported six cases of a unique form of uveitis that had not been described before. They named this clinical entity "Kirisawa Uveitis" after their professor, Nagamori Kirisawa. The report was the first documentation of ARN syndrome. The first international literature on acute retinal necrosis was by Willerson et al. [2] in the American Journal of Ophthalmology in 1977. Young and Bird coined

bilateral acute retinal necrosis (BARN) [3] 1978. Culbertson et al. [4] 1982 demonstrated the presence of the herpes virus in an enucleated eye of an ARN patient by electron microscopy in 1986. Varicella zoster was cultured from an ARN patient. In 1994 American uveitis society proposed diagnostic criteria for ARN syndrome.[5]

Standard Diagnostic Criteria for Acute Retinal Necrosis.[5]

The American uveitis society recommended diagnostic criteria for all clinical and laboratory studies in acute retinal necrosis in 1994.

1. Focal, well-demarcated areas of retinal necrosis located in the peripheral retina (outside the major temporal vascular arcade).
2. Rapid, circumferential progression of necrosis (if antiviral therapy has not been administered)
3. Presence of evidence of occlusive vasculopathy

4. Prominent inflammatory reaction in the vitreous and anterior chamber

Characteristics that support but are not required for diagnosis are 1. optic atrophy, 2. scleritis 3. pain.

ARN was first reported in Japan, now reported throughout the world. ARN affect both genders but has slight male preponderance. Acute retinal necrosis affects all age groups and a bimodal age distribution peaks at the 16-25 and 45-65 age groups. Bilateral involvement occurs in one-third of patients; usually, fellow eye involvement occurs between 1-6 weeks. A delay of several weeks to years had been reported to occur in the fellow eye.

The main etiological factor for acute retinal necrosis is the herpes family virus, of which alpha herpes virus Herpes simplex virus 1 (HSV1), Herpes simplex virus 2 (HSV2), and Varicella zoster (VZV) cause ARN most commonly. Rarely are Epstein-Barr virus (EBV) and Cytomegalovirus (CMV) implicated in causing ARN. ARN may result from a dormant HSV1, HSV2 or VZV viral reactivation in the retina. Since the causative viruses are neurotropic, the probable route for reaching the retina is to travel down the optic nerve. Alternatively, one of the other cranial nerves supplying the eye may transport the virus. The exact etiology of this reactivation remains elusive. However, an Immuno genetic predisposition to the disease is likely. HSV1, HSV2 and VZV were found in ocular samples in high copy numbers suggesting active viral replication in patients with ARN. Evidence suggests that primary viral infection, in addition to a secondary reactivation, can cause ARN. In such cases, the virus can reach through a haematogenous route, with infected lymphocytes enabling the virus to cross the blood-retinal barrier.

Treatment

In the years following the initial break linking the herpes virus to ARN, antiviral agents became the main treatment stay along with adjuncts like oral and topical corticosteroids, anticoagulants and cycloplegics.

The standard of antiviral therapy is intravenous (iv) administration of acyclovir. Newer oral antiviral agents are emerging as alternatives to high-dose intravenous acyclovir, avoiding the need for invasive and inpatient treatment. Combined oral and intravitreal antiviral therapy is gaining popularity. Drug resistance is uncommon and also difficult to identify. Antiviral drugs have few side effects, but special attention needs to be paid to patients with underlying renal disease in pregnant and immunocompromised patients.

The exact duration of treatment is still not conclusive. Newer methods, such as quantitative assays for viral DNA, may provide additional information and guide treatment in future.^[6,7]

Aim of the Study

To compare the treatment outcomes and long-term complications in ARN patients treated with only oral and combined antiviral therapy.

Objectives

1. Find the rate of occurrence of retinal detachment in Acute retinal necrosis patients treated with oral and combined antiviral therapy.
2. To study the treatment outcome regarding visual acuity in Acute retinal necrosis patients treated with oral and combined antiviral therapy.

MATERIALS AND METHODS

Prospective, observation, hospital-based case series study method.

Patient recruitment started after the institute review board (Ethical committee) approved the study. Informed consent was obtained from all participants of the study. The patient was recruited into the study if they had clinical features as described in standard diagnostic criteria by the American Uveitis Society 1994.^[5] A detailed history was obtained from the patient regarding his ocular complaints, mainly his symptoms at presentation and history regarding any viral infection suffered by the patient. If present, the type of viral infection was documented. Associated systemic illness was documented, particularly AIDS, as patients with AIDS are grouped as immunocompromised otherwise, patients are grouped as immunocompetent.

A data sheet was prepared to record the patient's demographic data 1. Age, 2. Gender, and 3. laterality of the eye involved.

Patients diagnosed with Acute retinal necrosis clinically, if needed, are investigated with USG B scan to rule out retinal detachment and ocular coherence tomography (OCT) to look for any macular involvement. A systemic investigation like Hemoglobin, total blood count, differential blood count, erythrocyte sedimentation rate, platelet count, and urine analysis was done. ELISA for Human immunodeficiency virus was done to find the patient's immune status with the patient's consent if needed.

Serial Fundus photography was taken to document the improvement of the disease after treatment.

Treatment

Patients were given oral antiviral therapy as a sole or combined antiviral therapy at the treating physician's discretion. In Oral antiviral therapy(Group1), T.Valacyclovir 1000mg TDS/ day was given for 8 to 12 weeks. Combined antiviral therapy (Group 2) includes a combination of oral antiviral, intravitreal antiviral, intravenous antiviral, and intravitreal antiviral. Intravitreal antiviral was given in Gancyclovir 2000µg in 0.1ml and intravenous antiviral as Inj. Acyclovir 5-10mg/kg TDS/day for 55 days. All patients are treated with cycloplegic and T.Prednisolone 1mg/kg per day in titrated dose as per the response.

Complications And Its Management

The most common complication in Acute retinal necrosis is RETINAL DETACHMENT. The time

gap of occurrence of retinal detachment from the onset of acute retinal necrosis was documented.

Follow-Up: All patients followed up for six months. Visual acuity, intraocular pressure, and a complete ocular examination were carried out during all follow-up visits complication, if any, was documented and treated appropriately. At the end of six months, the final best corrected visual acuity was recorded.

RESULTS

21 eyes of 18 patients studied, 11 (61.11%) were males, and seven (38.89%) were females. Bilateral involvement was seen in 3 patients (14.28%).

Treatment

15 eyes were given oral valacyclovir as the sole antiviral (Group 1), and six eyes were given combined antiviral therapy (Group 2)

Group 1(oral therapy) = 71.43%

Group 2(combined therapy) = 28.57%

Progression to Retinal Detachment

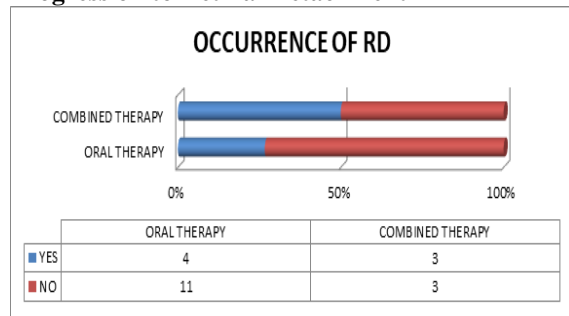


Figure 1: Occurrence of RD

In oral therapy, four eyes (26.67%) out of 15 eyes progressed to retinal detachment, and three eyes out of 6 (50%) progressed to retinal detachment in a combined therapy group.

The P value 0.354 (>0.05) says there is no association between the groups in the Progression to RD.

A total of 7(33.33%) patients progressed to retinal detachment on the whole.

Vision Analysis

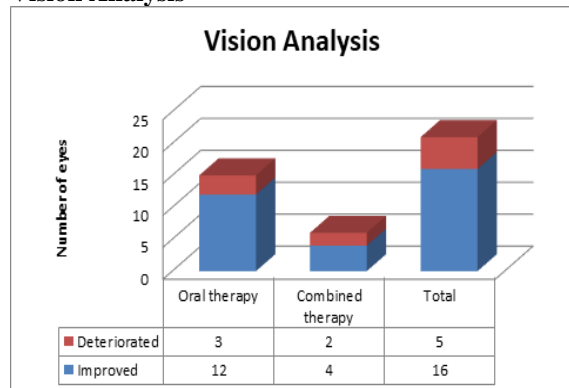


Figure 2: Vision analysis

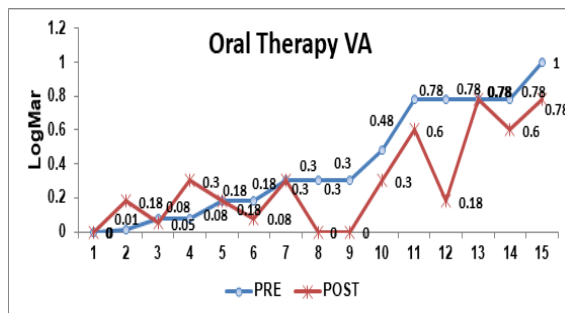


Figure 3: Oral therapy VA

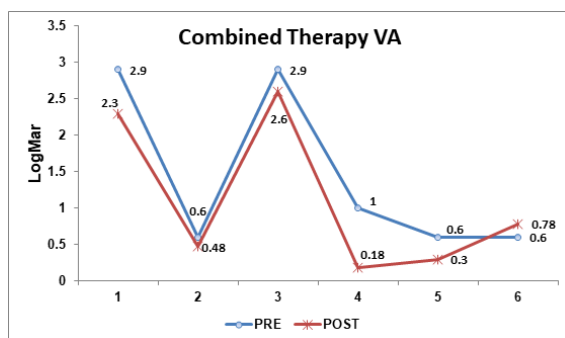


Figure 4: Combined therapy VA

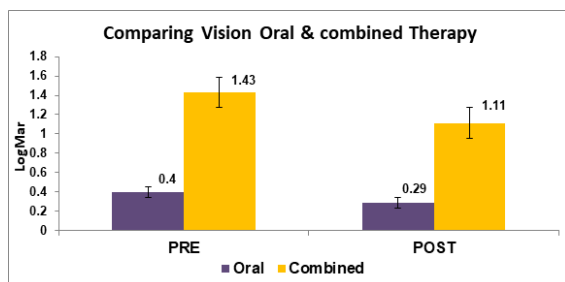
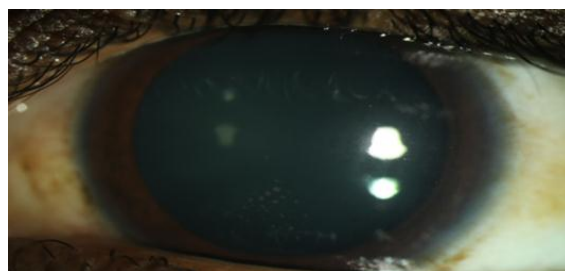
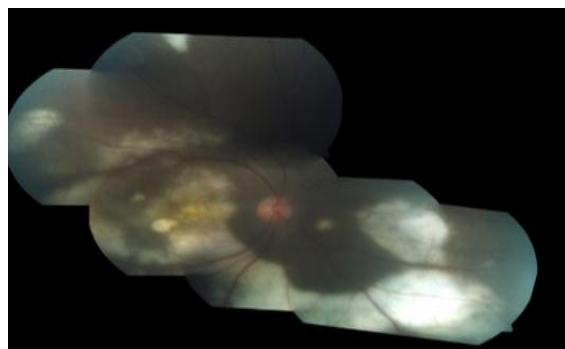


Figure 5: Comparing vision oral & combined therapy



Picture 1: Arrow indicating fresh Granulomatous keratic precipitates in ARN patient



Picture 2: Fundus montage of ARN patient showing Retinal necrosis

Table 1: Progression to RD

Group	Progression to RD		Total	P value
	No F (%)	Yes F (%)		
ARN Oral Therapy	11 (73.33)	4 (26.67)	15 (100)	0.354
Combined Therapy	3 (50)	3 (50)	6 (100)	
Total	14	7	21 (100)	

Table 2: Visual acuity

Visual Acuity	ARN Oral Therapy			Combined Therapy			P value#
	N	Mean (SD)	Range	N	Mean (SD)	Range	
Initial Vision	15	0.4(6/15) 0.33	0(6/6) – 1(6/60)	6	1.43(6/150) 1.14	0.6(6/24) – 2.9(PL)	0.02
Final Vision	15	0.28(6/12) 0.27	0(6/6) – 0.78(6/36)	6	1.1(6/75) 1.06	0.18(6/9) – 2.6(HM)	0.04
P value @	0.033			0.07			

The P values 0.02 and 0.04 are less than 0.05, meaning there is a statistically significant difference between the initial vision and final vision of the two groups.

The P value 0.033 <0.05 says a statistically significant difference exists between the initial and final visions of the ARN oral therapy group.

The P value 0.07>0.05 says no statistically significant difference exists between the combined therapy group's initial and final visions.

DISCUSSION

Treatment

In our study, patients have treated with oral valacyclovir 1000mg per day (given for approximately 8 to 12 weeks) or treated with intravenous acyclovir 10mg/kg 3 times per day for five days and followed with oral valacyclovir 1000mg 3 times per day. In addition to intravenous and oral acyclovir, a few patients were given intravitreal Ganciclovir 2000µg in 0.1ml. Patients treated with oral valacyclovir as the sole antiviral administered are grouped as oral therapy patients. Patients treated with two or more routes of antiviral are grouped as combined therapy groups. In our study, 15 out of 21 eyes (71.43%) were treated with oral therapy, and 28.57% of an eye (6 eyes) were treated with combined therapy. All patients, besides antiviral, received oral and topical prednisolone and cycloplegic. The treatment was administered at the treating ophthalmologist's discretion.

Emerson et al., in the year 2006, reported about treating ARN with oral valacyclovir/famciclovir as the sole antiviral.

In our study, no patients underwent prophylactic lasers.

Retinal Detachment

The necrosis, over time, would progress to retinal detachment. The detachment may be Exudative, rhegmatogenous or a combination of above mentioned two factors. Our study reports the overall occurrence of retinal detachment to be 33.33% (7 out of 21 eyes suffered RD. Compared to the literature collected, retinal detachment was lower in our study. In the analysis of patients who suffered retinal detachment, it was found that oral therapy patients progressed to retinal detachment less (26.67%) than combined therapy patients (50%). It was also found a

no statistical significance exists between both groups (P=0.354)

Vision Analysis

Acute retinal necrosis is a potentially blinding disease. Protection of vision is the primary aim of the treatment of the disease. The patient's vision was monitored during all visits. Best corrected visual acuity is recorded by Snellens chart and converted to LogMar scale for statistical analysis. Patient vision is said to deteriorate if his final vision is less than his vision at presentation, and vision is said not to deteriorate if the patient's final vision at the end of six months follow-up remains the same or improved compared to his initial vision at presentation.

The overall visual acuity of all eyes studied had improved significantly at the end of six months of treatment. Our study found that in 23 eyes (79.39%), the vision had not deteriorated, and in 6 eyes (28.61%), the vision had deteriorated.

Our study found the mean initial visual acuity in the oral antiviral therapy group was 0.40 LogMAR±0.33(1SD), and the mean final visual acuity was 0.28±0.27LogMar. A statistically significant (P=0.033) improvement in visual acuity between initial and final vision in oral therapy. Cochrane et al. [11] reported that the final mean visual acuity of patients treated with oral antiviral was only 0.89± 0.79 LogMar.

No statistically significant (P=0.07) improvement in visual acuity was noted between initial (mean= 1.43LogMar±1.14 (1SD)) and final visual acuity (mean 1.10±1.03LogMar in combined antiviral therapy group. Flaxel et al. [12] reported in combined antiviral therapy, mean visual acuity improved from 1.01±0.61 LogMar to 0.59±0.51LogMar.

A statistically significant (P=0.02) exists between mean initial visual acuity between oral and combined therapy. Mean initial visual acuity was better in an oral group than combined group.

Limitations in our Study

- Acute retina necrosis is a rare disease, the study sample was small, and the follow-up period was short. If the follow-up period was extended, more complications may be found.
- Sole oral antiviral therapy was started on patients with indolent acute retinal necrosis, and combined therapy was started in more severe cases. This results in differences in both initial and final visual acuity.

CONCLUSION

Acute retinal necrosis is a rare but potentially blinding disease. Polymerase chain reaction on ocular fluids helps to identify viral DNA, and appropriate treatment can be instituted. Prompt diagnosis and a good therapeutic approach are a must for better visual recovery. Vision-threatening complications like retinal detachment can be prevented with reasonable monitoring of ARN patients and prompt treatment. Oral antiviral and intravitreal antiviral are increasingly used in the treatment of ARN. Primary treatment with oral antiviral for indolent ARN is an effective alternative to combined therapy as the latter is invasive and requires hospitalization.

REFERENCES

1. Urayama A. Unilateral acute uveitis with periarteritis and detachment. *Jpn J Clin Ophthalmol* 1971;25:607–19.
2. Willerson D Jr, Aaberg TM, Reeser FH. Necrotizing vaso-occlusive retinitis. *Am J Ophthalmol* 1977;84:209–19.
3. Young NJ, Bird AC. Bilateral acute retinal necrosis. *Br J Ophthalmol* 1978;62:581–90.
4. Culbertson WW, Blumenkranz MS, Haines H, Gass DM, Mitchell KB, Norton EW. The acute retinal necrosis syndrome. Part 2: Histopathology and etiology. *Ophthalmology* 1982;89:1317–25.
5. Holland GN. Standard diagnostic criteria for the acute retinal necrosis syndrome. Executive Committee of the American Uveitis Society. *Am J Ophthalmol* 1994;117:663–7.
6. Ohtake-Matsumoto A, Keino H, Koto T, Okada AA. Spectral-domain and swept-source optical coherence tomography findings in acute retinal necrosis. *Arbeitsphysiologie* 2015;253:2049–51.
7. Tam PMK, Hooper CY, Lightman S. Antiviral selection in the management of acute retinal necrosis. *Clin Ophthalmol* 2010;4:11–20.
8. Abe T, Sato M, Saigo Y, Tamai M. Interferon-gamma expression and clinical features in patients with acute retinal necrosis syndrome. *Arbeitsphysiologie* 2003;241:982–7.
9. Guo L-B, Sun D, Ye J-J, Geng S, Xu H-Y, Zhang M-F. Intravitreal injection of Ganciclovir in the treatment of acute retinal necrosis. *Zhonghua Yan Ke Za Zhi* 2007;43:631–7.
10. Muthiah MN, Michaelides M, Child CS, Mitchell SM. Acute retinal necrosis: a national population-based study to assess the incidence, methods of diagnosis, treatment strategies and outcomes in the UK. *Br J Ophthalmol* 2007;91:1452–5.
11. Cochrane TF, Silvestri G, McDowell C, Foot B, McAvoy CE. Acute retinal necrosis in the United Kingdom: results of a prospective surveillance study. *EYE* 2012;26:370–7; quiz 378.
12. Flaxel CJ, Yeh S, Lauer AK. Combination systemic and intravitreal antiviral therapy in the management of acute retinal necrosis syndrome (an American Ophthalmological Society thesis). *Trans Am Ophthalmol Soc* 2013;111:133–44.
13. Meghpara B, Sulkowski G, Kesen MR, Tessler HH, Goldstein DA. Long-term follow-up of acute retinal necrosis. *Retina* 2010;30:795–800.
14. Hillenkamp J. Diagnosis and therapy of acute retinal necrosis. *Ophthalmologie* 2009;106:1057.
15. Roy R, Pal BP, Mathur G, Rao C, Das D, Biswas J. Acute retinal necrosis: clinical features, management and outcomes—a 10-year consecutive case series. *Ocul Immunol Inflamm* 2014;22:170–4.
16. Emerson GG, Smith JR, Wilson DJ, Rosenbaum JT, Flaxel CJ. Primary treatment of acute retinal necrosis with oral antiviral therapy. *Ophthalmology* 2006;113:2259–61.