# Comment on: Acute Retinal Necrosis: Virological Features Using Quantitative Polymerase Chain Reaction, Therapeutic Management, and Clinical Outcomes

EDITOR:

WE READ WITH GREAT INTEREST THE ARTICLE BY HAFIDI and associates[1] in the December 2019 issue of the *Journal* on the subject of acute retinal necrosis (ARN). This was a retrospective study of 24 patients treated with prolonged intravenous and intensive intravitreal antiviral therapy, with a median of 9 intravitreal injections. Treatment was tailored to measurements of aqueous viral load by quantitative real-time polymerase chain reaction (qPCR). The authors conclude that the low rate of retinal detachment compared with historical control subjects could be explained by the intensive course of intravitreal injections administered to many patients. We commend the authors on their outcomes but maintain several reservations regarding their methodology and conclusions.

The clinical utility of qPCR for viral load in ARN remains incompletely understood, and the benefit of continuing intravenous or intravitreal pharmacotherapy to achieve a "negativation" has not been demonstrated in a controlled trial. Clinical improvement and resolution can occur before the reduction of viral load in herpes virus infections, as nucleoside analogs such as acyclovir and ganciclovir inhibit viral replication but are not virucidal. In the referenced study by Bernheim and associates,[2] clinical healing defined by pigmentary changes within areas of retinitis occurred in every patient where there was a view to the fundus between 16 and 21 days, while viral DNA was detectable beyond 50 days. Similarly, in a case report of ARN from herpes simplex virus type 2, viral load from the vitreous was measured at 1379 DNA copies/mL 6 months after presentation and long after resolution of retinitis.[3] The interpretation of viral load in ARN merits further study, but persistent viral DNA should not be assumed to represent an indication for continued intravenous or intravitreal therapy.

In the present study, the duration of intravitreal as well as intravenous therapies deviated substantially from conventional protocols. Though it has never been validated in a randomized trial, the traditional treatment for ARN is intravenous acyclovir (10 mg/kg) every 8 hours for 7-10 days, followed by oral antiviral therapy. Further, oral therapy with valacyclovir has been accepted as an alternative to intravenous acyclovir in the absence of central nervous system disease.[4] As median duration of intravenous antiviral therapy was 24 days, it is difficult to draw conclusions regarding the utility of the intensive intravitreal injection regimen.

In keeping with American Academy of Ophthalmology's Ophthalmic Technology Assessment on ARN, we recommend induction therapy with high-dose oral valacyclovir with adjunct intravitreal foscarnet.[4] Numerous studies have shown that high-dose valacyclovir yields a comparable serum area under the curve compared to intravenous 10 mg/kg acyclovir, and several level II and III studies support initial oral antiviral therapy for ARN. Such treatment has numerous advantages compared to the discussed protocol: few strains of herpes viruses are resistant to foscarnet, and the use of oral induction therapy avoids the substantial costs of prolonged intravenous therapy, not to mention the costs of serial qPCR.

Without additional controlled studies comparing qPCR-guided treatment to a more traditional approach, we continue to recommend therapies supported by the American Academy of Ophthalmology's Ophthalmic Technology Assessment.

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# Reply to Comment on: Acute Retinal Necrosis: Virological Features Using Quantitative Polymerase Chain Reaction

EDITOR:

THE AIM OF OUR ARTICLE WAS TO PRESENT OUR CLINICAL experience with an aggressive treatment, and the results,

even if from a retrospective study, are interesting in terms of visual acuity and the low level of retinal detachment. We are fully aware of the bias a retrospective study presents and we would like to take the opportunity to discuss the different points highlighted by Taubenslag and Kim.[1]

Regarding the significance of the viral loads obtained by quantitative polymerase chain reaction, this certainly does not attest active viral replication; to prove this, retinal biopsy specimens would need to obtained, which is not possible. However, from our point of view, with such significant viral loads (≤1,000 copies/mL) and considering the clearance of aqueous humor, the positive polymerase chain reaction results cannot only correspond to noninfectious viral DNA elimination. This certainly supports the presence of viral activity. In the absence of consensual treatment, the monitoring of viral loads strikes us as an important tool to evaluate therapeutic response and to guide the course of treatment.

As for the implementation of only systemic treatment, the presence of occlusive retinal vasculitides that are common among cases of acute retinal necrosis are responsible for the lower bioavailability at the target site and reduced effectiveness of such drugs. Treatment by intravitreal injection allows for direct administration of the drug at the site of retinal necrosis, even in the presence of arterial occlusion. This is supported by Schoenberger and associates,[2] who report better results in terms of visual acuity and retinal detachment after the combined treatment of both systemic acyclovir and intravitreal injections of foscarnet, rather than systemic therapy alone.

Lastly, we consider viral reactivation inducing retinal necrosis to be a central nervous system manifestation and we therefore treat it as such with an intravenous treatment and not only by oral antiviral medication. Certainly, the cost is higher, but in our experience, we obtain better functional results and less frequent retinal detachment.

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SEE THE ORIGINAL ARTICLE FOR ANY DISCLOSURES OF THE authors.

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# Comment on: Retinal and Corneal Neurodegeneration and Its Association to Systemic Signs of Peripheral Neuropathy in Type 2 Diabetes

EDITOR:

WE READ WITH INTEREST THE STUDY "RETINAL AND corneal neurodegeneration and its association to systemic signs of peripheral neuropathy in type 2 diabetes" by Hafner and associates.[1] The authors have evaluated macular and peripapillary retinal nerve fiber layer in patients with various grades of diabetic retinopathy (DR) using optical coherence tomography (OCT), and have correlated these changes to corneal nerve length/density measured with confocal microscopy, clinical diabetic peripheral neuropathy (DPN) scores, and intraepidermal nerve fiber density (IENFD) measured with skin punch biopsy scores from the leg.

The authors have cited few previous studies that have indicated a strong role for corneal confocal microscopy as a surrogate marker of DPN.[1,2] However, the authors found no or very poor relation between IENFD and corneal neuronal parameters studied. Can this be because of the different nature of the 2 nerves being studied, the corneal nerve being a cranial nerve? In general, DPN is considered a symmetric form of diabetic neuropathy, whereas cranial nerve changes are a reflection of "asymmetric" cranial neuropathy. Other authors have classified DPN separately as a metabolic-microvascular-hypoxic type of neuropathy, while diabetic cranial neuropathy has been classified as inflammatory-immune type.[3]

In the perspective of retinal neuronal degeneration, the process can involve the retina at 3 different junctures: photoreceptors, middle retinal layers, and the inner retinal layers.[4,5] We have previously shown with electroretinogram that retinal neuronal degeneration affects all the layers of the retina at the outset of clinical DR, but as disease advances, middle retinal neuronal layers get more affected.[4] The current study has not used electrophysiology/corneal aesthesiometer to assess the functional nature of ocular neuronal loss, which, as they cite, is agreeably tedious.[1] However, as they have used OCT, middle retinal layers can be assessed at least morphologically and this may add further value to their analysis.

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