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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REFERENCES

1. Hafidi M, Janin-Manificat H, Denis P, et al. Acute retinal necrosis: virological features using quantitative polymerase chain reaction, therapeutic management, and clinical outcomes. *Am J Ophthalmol* 2019;208:376–386.
2. Bernheim D, Germi R, Labetoulle M, Romanet JP, Morand P, Chiquet C. Time profile of viral DNA in aqueous humor samples of patients treated for varicella-zoster virus acute retinal necrosis by use of quantitative real-time PCR. *J Clin Microbiol* 2013;51(7):2160–2166.
3. Cottet L, Kaiser L, Hirsch HH, Baglivo E. HSV2 acute retinal necrosis: diagnosis and monitoring with quantitative polymerase chain reaction. *Int Ophthalmol* 2009;29(3):199–201.
4. Schoenberger SD, Kim SJ, Thorne JE, et al. Diagnosis and treatment of acute retinal necrosis: a report by the American Academy of Ophthalmology. *Ophthalmology* 2017;124(3):382–392.

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