Commentary: Iatrogenic cytomegaloviral retinitis following intravitreal steroid implantation

Intravitreal Ozurdex [IO] steroid implant is used in diabetic maculopathy,[1] pseudophakic cystoid macular edema,[1] macular edema due to retinal venous occlusion,[1] and steroid cover in uveitic cataract for noninfective settings. However, its property of altered local immunity can trigger reactivation of fulminant latent infections such as cytomegalovirus retinitis (CMVR), acute retinal necrosis, and toxoplasmosis. This risk is amplified in immunosuppressed individuals such as those with bone marrow transplantation, cancer chemotherapy, uncontrolled diabetes, and malignancies. Specific prophylaxis against each of the opportunistic infections is not feasible. There are no proven randomized controlled trials to prove the superior efficacy of steroid implants over their alternatives. Hence, diligent care in case selection assumes significance.

In one of the largest trials on IO, namely the GENEVA study,[2] exclusion criteria did not include patients on systemic immunosuppression though subjects on systemic steroids were excluded from the study. Vannozzi *et al*. had postulated that, in retinal vein occlusion, the retinal blood flow stasis and the breakdown in the blood–retina barrier may increase the susceptibility of ocular tissues to virus penetration, especially with diabetic vasculopathy being a facilitator of CMVR.[3,4]

In the management of CMVR ,apart from the treatment per se, the risk factors that had set the stage of retinitis needs to be addressed and treated. Thorough investigations to rule out the differentials such as acute retinal necrosis, toxoplasmosis, tuberculosis, and syphilis and support that the diagnosis of CMVR needs to be done. In the standard regimen for CMVR with the induction phase on parenteral/oral antivirals, the treatment response is closely monitored with autofluorescence and color fundus photographs. This aids in the treatment decision on the transition from induction to continuation phase as well as for the finite end point. Although intravitreal ganciclovir as a local injection or as implant can be supplanted, it does not prevent the fellow eye involvement or the systemic events.[5]

Ideally, quantitative and qualitative polymerase chain reaction (PCR) done before and after the treatment aids in assessing the response and plan a finite endpoint. However, clinical treatment should not be withheld pending its results. An important caveat is that the sensitivity of the PCR for CMV reduces after the antivirals are initiated.[6] PCR results are not immune from false positivity as well as negativity and should be interpreted with caution. Since the duration of anti-inflammatory action of IO lasts for 3–6 months after injection, it is important to closely monitor and add

prophylactic antivirals in the maintenance dose straddling their action duration to prevent any viral reactivation. Following IO, when CMVR develops, there is a lucid transition from the indication of the implant to its exact contraindication! Hence, removal of IO for all such cases is a controversial option worth considering, especially for severe Zone 1 cases, given the medicolegal significance. Literature review of the cases in which explantation of Ozurdex is not considered had their limitations. They include the milder ones with Zone 2 involvement, lack sufficient follow up straddling the duration of IO resulting in poorer final visual outcomes.[3] On the contrary, explantation of IO eliminates local immunosuppression that acted as an inciting event. The priority shifts to the treatment of CMVR, the contraindication of IO over its original indication. With no feasible randomized control trial to prove this point, the clinician needs to keep this option open.

Resistance to ganciclovir in UL97 gene mutation must be considered in persistent active retinitis despite 6 weeks of induction therapy. It is tackled by combining foscarnet with ganciclovir or adding a combination therapy of ganciclovir implant/intravitreal injection to the systemic therapy.[7] Intravitreal cidofovir is not indicated due to its low therapeutic window.[7]

Fundamentally, the parameter of CD4 levels below 50 is a risk factor of acquiring CMVR. Conversely, the improved CD4 levels need not parallel the clinical resolution of retinitis due to the pivotal role for CMV-specific antibodies. Its quantification in the vitreous before the end point can be considered as a possible future research tool.

The readers should delineate the related entity namely "immune recovery uveitis" that develops in CMV retinitis with a triad of cystoid macular edema, epiretinal membrane, and cataract. This follows reconstitution of CD4 levels when retinitis becomes inactive. It is a diagnosis of exclusion when alternate etiologies are ruled out and merits adding steroids orally and locally.[4]

Besides the more common infective uveitis in a developing world, the risk of acquired infections clearly persists in noninfective uveitis too when on immune modulators. Beware that any long-acting steroid implant like IO is a steroid and cautiously interprets any study results to adapt in our practice!

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References

1. Kapoor KG, Wagner MG, Wagner AL. The sustained-release dexamethasone implant: Expanding indications in vitreoretinal disease. Semin Ophthalmol 2015;30:475-81.
2. Haller JA, Bandello F, Belfort R Jr., Blumenkranz MS, Gillies M, Heier J, *et al.* Dexamethasone intravitreal implant in patients with macular edema related to branch or central retinal vein occlusion twelve-month study results. Ophthalmology 2011;118:2453-60.
3. Vannozzi L, Bacherini D, Sodi A, Beccastrini E, Emmi G, Giorni A, *et al*. Cytomegalovirus retinitis following intravitreal dexamethasone implant in a patient with central retinal vein occlusion. Acta Ophthalmol 2016;94:158-60.
4. Shah AM, Oster SF, Freeman WR. Viral retinitis after intravitreal triamcinolone injection in patients with predisposing medical comorbidities. Am J Ophthalmol 2010;149:433-400.
5. Musch DC, Martin DF, Gordon JF, Davis MD, Kuppermann BD. Treatment of cytomegalovirus retinitis with a sustained-release ganciclovir implant. The Ganciclovir Implant Study Group. N Engl J Med 1997;337:83-90.
6. McCann JD, Margolis TP, Wong MG, Kuppermann BD, Luckie AP, Schwartz DM, *et al.* A sensitive and specific polymerase chain reaction-based assay for the diagnosis of cytomegalovirus retinitis. Am J Ophthalmol 1995;120:219-26.
7. Stewart MW. Optimal management of cytomegalovirus retinitis in patients with AIDS. Clin Ophthalmol 2010;4:285-99.

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