

## Comment on “Insights into the pathogenesis of cystoid macular edema: leukostasis and related cytokines”

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Received: 2019-08-24 Accepted: 2019-09-24

**DOI:10.18240/ijo.2020.08.25**

**Citation:** Cimolai N. Comment on “Insights into the pathogenesis of cystoid macular edema: leukostasis and related cytokines”. *Int J Ophthalmol* 2020;13(8):1343-1344

**Dear Editor,**

The review of Chung *et al*<sup>[1]</sup> regarding the pathogenesis of cystoid macular edema (CME) raises valid postulates of shared pathogenesis which is based on inflammation and associated permeability. Albeit recognizing diverse etiological conditions, the definition of common pathways has the potential to improve interventionist strategies. One further mechanism for CME that is less appreciated, however, is the cascade of reactions induced or modulated by eicosanoids.

As an example, prostaglandin F<sub>2</sub>alpha (PGF<sub>2</sub>α) can have a pathological role in both acute and chronic inflammation<sup>[2]</sup>. PGF<sub>2</sub>α can also serve as a biomarker of oxidative stress and inflammation<sup>[3]</sup>. Following the discovery that the topical ocular application of several prostaglandins could reduce intraocular pressure in animal models, PGF<sub>2</sub>α was assessed in normotensive adults<sup>[4]</sup>. PGF<sub>2</sub>α reduced intraocular pressure and did not seemingly produce aqueous flare or anterior chamber cellular responses, but was nevertheless deemed causative of lower eyelid reddening, symptomatic ocular irritation, conjunctival hyperemia, and headache<sup>[4]</sup>. Shortly thereafter, it was hypothesized that prostaglandins were sentinel to the genesis of epinephrine maculopathy and aphakic CME<sup>[5]</sup>. As a by-product of the latter research, the development of PGF<sub>2</sub>α analogues as a treatment for glaucoma was encouraged. Several such analogues (*e.g.*, unoprostone, latanoprost, travaprost, bimatoprost) were clinically applied and represented a novel and very important arm in the

therapeutics of increased intraocular pressure reduction. To this day, efficacy has been ascribed to an increase in the outflow of aqueous humor at the uveoscleral interface. PGF<sub>2</sub>α and its analogues were also found to induce the local release of various endogenous prostaglandins<sup>[6]</sup>.

Soon after clinical introduction, PGF<sub>2</sub>α analogues were being associated with iatrogenic CME induction, albeit for a minority of treated patients<sup>[7-8]</sup>. Whereas an interruption of the blood-retinal barrier was proposed as a mechanism for the latter toxicity, some contended that reagent preservative was causative<sup>[7-8]</sup>. Since then, a number of very convincing case reports have continued to raise concern with PGF<sub>2</sub>α analogues and CME causation<sup>[9]</sup>. Several reviews also continued to draw attention to this phenomenon<sup>[10-11]</sup>. The large, although retrospective, case-control study of Wendel *et al*<sup>[12]</sup> provides further support for a possible cause-and-effect relationship. Parallel to the above are studies which find that topical non-steroidal anti-inflammatory agents and corticosteroids, which have eicosanoid modulating effects, offer effective treatment of CME in some patients<sup>[13-14]</sup>.

The availability of PGF<sub>2</sub>α analogues lends itself to the establishment of disease in experimental models. Such a reliable model of disease would then allow researchers to further explore not only the role of eicosanoids in disease, but also potentially further research into pathogenetic events that may be in common with other causations of CME. Throughout, however, one must be cautious with the assumption that all CME events have a common pathology or not<sup>[15]</sup>. As well, co-factor events need consideration.

### ACKNOWLEDGEMENTS

**Conflicts of Interest:** Cimolai N, None.

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### Author Reply to the Editor:

#### Dear Editor,

We appreciate the thoughtful comments by Nevio Cimolai about our article “Insights into the pathogenesis of cystoid macular edema: leukostasis and related cytokines”. We also want to thank the editor for the chance to further discuss our article.

As Cimolai resumed in his comment, prostaglandins analogues can cause cystoid macular edema (CME) as an adverse event<sup>[1]</sup>. Prostaglandins are also known to be involved in the pathogenesis of pseudophakic CME (*i.e.*, Irvine-Gass syndrome)<sup>[2-3]</sup>. Prostaglandins are thought to be synthesized in the aqueous humor secondary to the stimulation of anterior

uveal or lens epithelial cells from operative irritation<sup>[3]</sup>. Subsequent disruption of the blood-aqueous barrier results in the dispersion of prostaglandins, cytokines, and other inflammatory cytokines in the vitreous, which in turn cause damage to the blood-retinal barrier<sup>[3]</sup>.

We agree that prostaglandins can cause CME, while this is one of initiating factors among various pathological conditions. It should be emphasized that CME is not a diagnosis but a finding occurring from numerous causes, *i.e.* a nonspecific sequela of many ocular diseases<sup>[4]</sup>. Initiating factors include preservatives in ophthalmic medications, topical prostaglandin analogs, topical beta-blockers, retinal vein occlusion, diabetic retinopathy, uveitis, retinitis pigmentosa, radiation retinopathy, posterior vitreous detachment, and so forth<sup>[1,3-8]</sup>. CME, whether it is iatrogenic or disease-related, may share a common pathology. Our review has focused on “common pathogenesises”: the pathogenesis of CME based on vasogenic mechanisms including vascular hyperpermeability, leukostasis, and inflammation, and then the cytotoxic mechanisms based on retinal Müller cell dysfunction. We do believe that the pathogenesis of CME caused by eicosanoids also falls into “common pathogenesises” described in our review.

Thank you again for your interest in our article.

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