Eye (2017) 31, 1744–1748

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CORRESPONDENCE

Sir,
Hydroxychloroquine and the eye: an old unsolved problem

We agreed with the conclusions of Latasiewicz *et al*[1] 'Hydroxychloroquine retinopathy: an emerging problem', which cited cases of hydroxychloroquine (HCQ)-induced retinal damage. Three patients had received 400 mg HCQ daily for over 15 years (equaling 4.93 mg/kg/day in two and 5.6 mg/kg/day in one) and all developed maculopathies of varying severity. The study by Latasiewicz *et al*[1] recommended a standardized screening protocol to monitor for retinal toxicity in patients treated with HCQ. Ocular toxicity ranged from non-significant keratopathy to a potentially blinding retinopathy as described previously with varying doses of HCQ.[1,2] In 2016 the American Academy of Ophthalmology recommended a maximum daily HCQ use of 5.0 mg/kg, a baseline fundal examination to exclude pre-existing maculopathy and an annual screening after 5 years of HCQ use.[3]

Being a synthetic antimalarial, HCQ is used for immunomodulation in autoimmune diseases.[2] Commonly used daily doses of HCQ are 200mg or 400 mg (which equals a dose of 5.3 mg/kg and 2.6 mg/kg for a 75 kg patient, respectively), and therapeutic plasma concentrations of 500–2000 ng HCQ/ml have previously been described.

The pathogenesis of HCQ-induced retinal toxicity is not fully understood. HCQ displays a high affinity to melanin containing cells in the skin, ciliary bodies, and retinal pigment epithelium (RPE).[2] Previous *in vitro* studies on cultured RPE cells suggest that HCQ causes retinal damage through changing RPE lysosomal pH, resulting in higher levels of lipofuscin, a pigment that commonly accumulates with age and is associated with photoreceptor degeneration.[2] Interestingly Bharadwaj *et al*[4] showed *in vitro* that leukocyte migration on retinal epithelium is linked to an increased expression of adhesion molecules (including intercellular adhesion molecule (ICAM-1)).

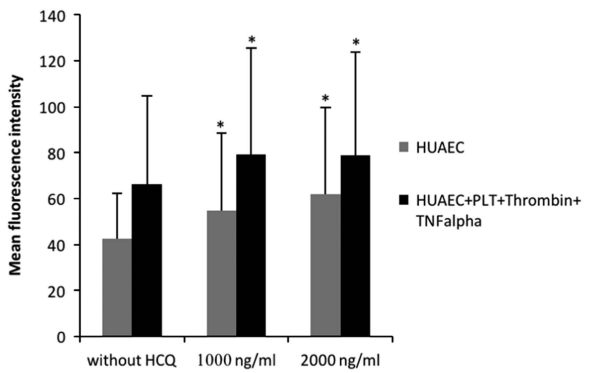

Figure 1 Surface expression of ICAM-1 on HUAEC with and without 24 h pre-incubation with 1000ng/ml or 2000 ng/ml HCQ. $N=7$; PLT, platelets; TNFalpha, tumor necrosis factor alpha (*$P<0.05$, as evaluated by Dunnett's test).

Our *in vitro* experiments are the first to link therapeutic levels of HCQ to increased ICAM-1 expression. In this model, HCQ-exposed human umbilical arterial endothelial cells are stimulated with tumor necrosis factor alpha and thrombin-activated platelets, and showed significantly elevated levels of ICAM-1 when HCQ doses of >1000 ng/ml are used (Figure 1). These results suggest that ICAM-1 may be involved in the pathogenesis of HCQ-induced retinal toxicity.

Conflict of interest

The authors declare no conflict of interest.

References

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Eye (2017) **31,** 1744; doi:10.1038/eye.2017.130; published online 14 July 2017

Sir,
Are techniques for general anesthesia less invasive than procedures for cataract surgery?

We read with special interest the retrospective cohort study by Alboim *et al*[1] who examined the importance of preoperative evaluation for outpatients undergoing cataract surgery. They suggested that preoperative evaluation has no role in reducing adverse events in these