was found to have no effect on the pharmacokinetics of CQ (Ette *et al.,* 1987b).

CQ impairs the antibody response to intradermal human diploid-cell rabies vaccine (Pappaioanou *et al.,* 1986). Hence, the vaccine should be administered intramuscularly in those taking CQ prophylaxis. CQ has also been associated with reduced antibody response to the *Vibrio cholerae* vaccine CVD103-HgR (Kollaritsch *et al.,* 1997). No effect on antibody responses to yellow fever vaccine was shown with concomitant CQ use (Barry *et al.,* 1991).

6. ADVERSE REACTIONS AND TOXICITY

CQ is extremely well tolerated when taken for the prevention or treatment of malaria. Minor side effects occur rarely and include nausea, vomiting, diarrhea, insomnia, headache, rash, and pruritus. Retinal toxicity may occur after prolonged use of CQ or HCQ, and monitoring is required. Neurotoxicity and cardiotoxicity have been reported but occur rarely. It is important to note, though, that CQ has an extremely narrow therapeutic range and is highly toxic in overdose.

6a. Dermatologic effects

Pruritus is the most common cutaneous side effect of CQ. In a survey of 777 students in Mozambique, CQ-induced pruritus occurred in 31% and 10% of those who had received CQ treatment or prophylaxis, respectively (Gama *et al.,* 2009). Skin pigmentation may also occur and is thought to be secondary to ecchymosis (Jallouli *et al.,* 2013). In a case–control study involving patients treated with HCQ for SLE, pigmentation occurred a median of 6 years (range 3 months–22 years) after commencement of HCQ therapy, and was associated with previous treatment with oral anticoagulants and/or antiplatelet agents, and with higher blood HCQ levels (Jallouli *et al.,* 2013). There was no association with duration of treatment or cumulative HCQ dose. Although improvement after cessation of treatment occurs in some cases (Jallouli *et al.,* 2013), persistence 1 year after treatment cessation has also been reported (Morrison *et al.,* 2008). It has been suggested that pigmentation may be associated with an increased risk of CQ- or HCQ-associated retinal toxicity (Bentsi-Enchill, 1980; Millard *et al.,* 2004).

A small number of cases of acute generalized exanthematous pustulosis (AGEP) have been reported in patients receiving HCQ for rheumatologic conditions (Paradisi *et al.,* 2008; Lateef *et al.,* 2009; Bailey *et al.,* 2012). Drug reaction with eosinophilia and systemic symptoms (DRESS) has been reported after a 2-week course of HCQ 400 mg daily for seronegative arthritis (Volpe *et al.,* 2008). Rare cases of toxic epidermal necrolysis (Murphy and Carmichael, 2001; Cameron *et al.,* 2014), and Stevens-Johnson syndrome (Leckie and Rees, 2002) have occurred.

Other dermatologic reactions reported with CQ or HCQ use include contact dermatitis, and phototoxic and photoallergic dermatitis (Pérez-Ezquerra *et al.,* 2006); vitiligo (Selvaag, 1997); and pemphigus (Ghaffarpour *et al.,* 2006).

6b. Ocular toxicity

Retinal toxicity is a potentially serious complication of long-term CQ and HCQ use. Although the mechanism of toxicity is uncertain, the binding of CQ and HCQ to melanin in the retinal pigment epithelium (RPE) likely contributes. CQ- or HCQ-induced retinal toxicity is characterized by bull's-eye maculopathy, a ring of RPE depigmentation with fovea sparing. Although visual acuity may be excellent, paracentral visual scotomas may develop. With continued drug exposure, the area of functional disturbance and RPE atrophy spreads into the fovea, with resultant loss of visual acuity, and eventually the entire fundus may be involved. Visible bull's-eye maculopathy is generally irreversible and may progress after the drug has been ceased. Delayed-onset retinopathy has also been reported, many years after cessation of CQ or HCQ (Martin *et al.,* 1978; Ehrenfeld *et al.,* 1986; Kazi *et al.,* 2013).

Although HCQ is associated with less retinal toxicity than CQ, the use of sensitive screening techniques has shown that the prevalence of HCQ retinopathy is more common than previously thought. In a review of 2361 patients who had used HCQ daily for 5 years or longer, the overall prevalence of HCQ retinopathy was 7.5% (Melles and Marmor, 2014). The prevalence varied with daily consumption (odds ratio: 5.67 [95% confidence interval (CI): 4.14–7.79] for > 5.0 mg/kg) and with duration (odds ratio: 3.22 [95% CI: 2.20–4.70] for > 10 years). For daily consumption of 4–5 mg/kg of real body weight, the prevalence of retinal toxicity was < 2% for the first 10 years of use, but increased to 20% after 20 years of use, with an annual risk of 4% thereafter. For patients using > 5 mg/kg/day, the risk of retinopathy was 10% at 10 years, and 40% at 20 years. Additional risk factors included kidney disease and concurrent tamoxifen therapy. Of note, dosage per real body weight was found to be a better predictor of retinal toxicity than dosage per ideal body weight.

Current guidelines from the American Academy of Ophthalmology recommend that all patients receiving long-term HCQ should undergo a detailed baseline ophthalmologic examination when the drug is started, with yearly follow-up commencing after 5 years of continuous therapy, or when a cumulative dose of 1000 g has been reached (Marmor *et al.,* 2011). Screening should include the use of at least one objective test if available, such as multifocal electroretinogram (mfERG), spectral domain optical coherence tomography (SDOCT), and fundus autoflourescence (FAF), in addition to visual field testing. Patient counseling should be undertaken to emphasize the risk of retinal toxicity and the need for regular examinations.

Other ocular side effects include corneal deposits, poor night vision, and reduced color vision, especially in the blue-yellow spectrum.

6c. Ototoxicity

Ototoxicity has been reported with both CQ (Hart and Naunton, 1964; Matz and Naunton, 1968; Hadi *et al.,* 1996)