error of ±0.5 mm Hg, this was considered to be very stringent, and studies have reported only 0% to10.3% of GAT in institutions fall within this range.[2,3] The clinically acceptable calibration error range was less than ±2.5 mm Hg.[3] If the latter was followed, then that might affect the outcome of this study significantly. Second, interobserver variability for GAT has been reported to be up to 4 mm Hg.[4,5] We believed choosing >4 mm Hg as the standard would reveal the real disagreement beyond the interobserver test-retest variability.

We agree with the authors that IOP is just a surrogate measurement of glaucoma and that we need to consider the entire picture, such as structural and functional changes, before making any major decisions.

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ALL AUTHORS HAVE COMPLETED AND SUBMITTED THE ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

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Reply to Comment on: Evaluating Goldmann Applanation Tonometry Intraocular Pressure Measurement Agreement Between Ophthalmic Technicians and Physicians

EDITOR:

WE APPRECIATE THE THOUGHTFUL COMMENTS OF DR. SHU and associates. The authors raise the concern that circadian rhythm may have partly contributed to the differences in intraocular pressure (IOP) when comparing clinicians to technicians. While it is theoretically possible, we doubt that this would have been the case in the present study as patients were evaluated by physicians within a short time of being screened by technicians. Although we did not collect data for the exact amount of time elapsed between IOP measurements taken by the technician and those taken by the physician, the longest it would have been was an hour, and most subjects would have been seen within minutes.

The authors also raise a concern about the calibration of tonometers in our clinics. We log these calibrations weekly, and all tonometers must meet a calibration error of ±0.5 mm Hg or they are sent for repair.

Finally, the authors suggest that random noise can produce differences of ±2 mm Hg when measuring IOP and suggest that a more appropriate cutoff value for the study would have been a difference of >4 mm Hg. Although these larger fluctuations are sometimes seen, we continue to believe that differences >2 mm Hg are important from a clinical standpoint and could result in altered treatment plans in some cases.

Once again, we thank Dr. Sahu and associates for raising these important considerations.

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Comment on: Rethinking the Hydroxychloroquine Dosing and Retinopathy Screening Guidelines

EDITOR:

WE READ WITH INTEREST THE STUDY BY BROWNING AND associates[1] and are writing to highlight the highly variable pharmacokinetics of hydroxychloroquine (HCQ) and its potential implications in HCQ-induced retinopathy (HCQR). The authors stated daily dosage was the most important and only modifiable risk factor for HCQR. Despite being the most important risk factor for HCQR, the dose itself does not completely predict HCQ exposure. HCQ has a variable and incomplete absorption (30%-100%).[2] The reported volume of distribution ranges from 153 liters to 47,247 liters.[2,3] HCQ is desethylated to *N*-desethylhydroxychloroquine (the major active metabolite), and 2 other metabolites in common with

chloroquine, desethylchloroquine and bidesethylchloroquine. From chloroquine, which differs from HCQ by just 1 hydroxyl group, it can be extrapolated that HCQ is possibly metabolized by the same cytochromes (CYPs) as those for chloroquine, that is, CYP2C8 and CYP3A and to a lesser extent by CYP2D6.[4,5] CYP2D6 polymorphism has been demonstrated to correlate with variations in HCQ metabolism among Korean lupus patients.[4] Another study also found metabolism of amodiaquine, which is structurally related to HCQ, to be impaired in patients with CYP2C8 polymorphisms.[6] Concurrent administration of drugs that are metabolized through CYP2C8, CYP3A4, and CYP2D6 (eg, metoprolol, fluoxetine, and venlafaxine) will compete with HCQ for metabolism and lead to increased levels of HCQ.[2]

The medical community is generally not aware of the pharmacokinetics of HCQ, as it is not well detailed in standard drug references. Clinicians should be aware of the variability of HCQ pharmacokinetics and understand that dose is just one of the many factors affecting drug exposure. Toward the end of their paper, the authors put forward the question of whether therapeutic drug monitoring could solve the dosage controversy by providing more direct guidance to prescribers. We agree that drug level, rather than drug dosage per se, better informs clinicians about actual HCQ exposure. Measuring drug level removes the uncertainty of drug exposure associated with the highly variable pharmacokinetics and drug interactions. However, therapeutic drug monitoring is reactive in nature. Precision of initial dosages could be optimized by taking into account factors such as genotyping (eg, the metabolizer status of CYP2C8). Future studies should explore the cutoff values of efficacy and toxicity for HCQ serum level and aim at providing evidence of benefit and safety with HCQ therapeutic drug monitoring. Researchers should also investigate incorporating genotyping in the dosage algorithm of HCQ as part of the effort to achieve personalized medicine.

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Reply to Comment on: Rethinking the Hydroxychloroquine Dosing and Retinopathy Screening Guidelines

EDITOR:

WE APPRECIATE THE COMMENTS FROM LAW AND ASSOCIates regarding our Perspective. They reiterate that pharmacokinetics (PK) of hydroxychloroquine (HCQ) are variable and that a daily dose produces variable blood concentrations depending on genetic factors, absorption variables, and effects of induction and inhibition of metabolizing enzymes, all topics that we reviewed in a previous publication.[1]

Both pharmacokinetics and the pharmacodynamics studies are helpful to determine the therapeutic dose. When HCQ was first approved in 1955, neither placebo-controlled trials nor formal PK/pharmacodynamic studies were performed. However, the current conventional dosage has evolved over decades of clinical use and largely demonstrates efficacy and long-term safety.[2,3] Recently, HCQ therapy, used at much higher-than-conventional dosages, has been tried for several nonrheumatic conditions. Two of 7 patients (28.6%) receiving 1,000 mg/day for non–small cell lung cancer[4] and 3 of 12 patients (25%) receiving 800 mg/day for chronic graft versus host disease[5] experienced early onset HCQ retinopathy. Meanwhile, in patients receiving 200-400 mg/day with a ceiling daily dose of 6.5 mg/kg, for the ideal body weight for patients with systemic lupus erythematosus, early onset HCQ retinopathy is rare, although it occurred in a patient with high blood level of HCQ.[6]

Law and associates recommend monitoring of therapeutic drug levels of HCQ. We agree that this will be more objective than monitoring daily prescribed dosages. However, there are few data relating drug levels, duration of exposure, and onset and progression of HCQ retinopathy. Until we have replicated research showing the relationship of drug level and retinopathy, some form of weight-based dosages will be prevalent in clinical practice, and guidelines will need to be refined as suggested in the Perspective.