Evidence-based Rheumatology

edited by M. Matucci Cerinic

Hydroxychloroquine at the recommended dose (≤6.5 mg/kg/day) is safe for the retina in patients with rheumatoid arthritis and systemic lupus erythematosus

Authors: I. Mavrikakis *et al.*
Title: The incidence of irreversible retinal toxicity in patients treated with hydroxychloroquine. Areappraisal
Source: *Ophthalmology* 2003; 110: 1321–6

Aim

The antimalarial drugs chloroquine and hydroxychloroquine (HCQ) (quinolones) are well-known and effective agents for the treatment of rheumatoid arthritis (RA), systemic lupus erythematosus (SLE) and other connective tissue and skin diseases, but beginning in the late 1950s reports have associated their use with the development of retinal toxicity (1). In order to determine the risk of hydroxychloroquine (HCQ)-related retinal toxicity in patients with RA and SLE, a prospective study (1985 – 2000) was performed in a cohort of Greek patients with RAand SLE who were treated with HCQ at the currently recommended dosages (≤ 6.5 mg/kg/ day). The greater part of the patients had completed at least 6 years of treatment. This work reports an extension of the study undertaken by the same group for the period 1985-1995 (2).

Methods

526 patients treated with HCQ (335 affected by RA and 191 by SLE) were enrolled. Criteria for inclusion were treatment for more than 1 year with HCQ and accurate drug dosage records. Exclusion criteria were previous exposure to chloroquine and renal or liver failure.

400 out of the 526 patients (239 RA and 161 SLE) studied had received long-term treatment (≥ 6 years). Among these the mean duration of therapy was 8.7 years (range: 6-16 years). In the remaining 126 patients, the mean duration of therapy was 3.1 years (range: 1-6 years). The daily HCQ dosages administered were ≤ 6.5 mg/kg in all patients.

An ophthalmologic evaluation was performed every 6 months from 1985 to 1995 (2), and yearly thereafter in these patients. This included the assessment of Snellen's best-corrected visual acuity, color vision testing with the Farnsworth D-15 panel test, Rodenstock central visual field testing, fundoscopy after pupil dilation, and full-field electroretinography (mixed rod and cone responses to 3-Hz white flashes and cone-isolated responses to a 50-Hz white flicker). Fluorescein angiography was also performed in patients with evidence of fundoscopic lesions. The main outcome measure was the presence of fundus lesions attributable to HCQ.

Results

No HCQ-related retinal toxicity was noted in any of the 400 patients on long-term treatment during the first 6 years, nor in the 126 patients treated with HCQ for a mean of 3.1 years. Two (3.4%) of the first 58 long-term (≥ 6 years) treated patients developed HCQ-related maculopathy after 8 and 6.5 years of treatment despite regular ophthalmologic evaluation. On follow-up, 7 and 9 years after cessation of HCQ, both patients had stable eye disease. No HCQ retinal toxicity was observed in the subsequent 342 patients who were treated for ≥ 6 years. Furthermore, no other cases were identified among the first 58 patients who continued taking the drug after 1995. Thus, the overall incidence of HCQ-related retinopathy in the 400 patients treated with recommended dosages of the drug who had completed a mean of 8.7 years of follow-up at the time of the analysis, was reduced to 0.5%.

Conclusion

HCQ is safe for the retina in patients being treated for RA and SLE. After a baseline ophthalmic examination to confirm the absence of fundus alterations, patients with normal renal function may take the maximum recommended dosage of the drug (6.5 mg/kg/day) and continue safely for 6 years. However, annual screening is recommended for patients who have been on HCQ, even at the recommended doses, for more than 6 years (3).

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Comment

Two years ago the American Academy of Ophthalmology published recommendations on screening for chloroquine and hydroxychloroquine (HCQ) retinopathy (1). This report by Mavrikakis et al. *elegantly confirms, from a large patient base, the basic conclusions that HCQ dosages below 6.5 mg/Kg/day are generally safe, although ophthalmologic screening is important at baseline (when the drug is started) and on an annual basis after 5 - 6 years of usage. Toxicity from HCQ is rare, but it still occurs (2) and, if it cannot be prevented, it needs to be recognized early because the retinal damage is usually irreversible.*

There are two important corollary issues to consider. The first concerns risk factors and HCQ dosage. Doses under 6.5 mg/Kg/day are not necessarily safe for individuals who have defective kidney or liver function (since these organs clear HCQ), who are elderly or who have underlying retinal dis - ease. This dosage is also too high for obese patients, since HCQ does not bind to fatty tissues (1). The rule really should say "keep daily dosage below 6.5 mg/Kg of lean body weight."

The second issue concerns methods of screening. Subjective measurements of vision are useful, but objective measures would be better. However, evaluations of retinal electrical activity (electroretinogram) in HCQ users have shown that many patients have abnormalities that do not correlate in

any clear way with other ophthalmologic signs of toxicity (3). It will be important to learn whether these electrical changes represent effects of the underlying rheumatoid disease, pharmacologic (but not toxic) actions of the drug, or toxicity. A new technique called multifocal electroretinography can measure local electrical activity across the central retina, and may prove a powerful tool for following patients on HCQ (4).

The message for rheumatologists: be aware of the proper dose levels for "lean" body weight -- and get the assistance of your ophthalmology colleagues for screening.

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ERRATUM CORRIGE

In our last issue the cited references were omitted from the comment of Prof. M. Cutolo on the paper by A. Weinblatt *et al*. We apologize for the oversight and herewith re-publish the comment in its entirety.

The addition of adalimumab to methotrexate reduces rheumatoid arthritis activity in patients with longstanding disease

Author: A. Weinblatt *et al*.
Title: Adalimumab, a fully human anti-tumor necrosis factor alpha monoclonal antibody, for the treatment of rheumatoid arthritis in patients taking concomitant methotrexate: The ARMADA trial.
Source: *Arthritis Rheum* 2003; 48: 35-45.

Comment

This study by Weinblatt et al. *on the fully human monoclonal TNFα antibody adalimumab presents further confirmation that TNFα blockade in rheumatoid arthritis (RA) is efficacious and well tolerated. The improvement was dose-related (i.e. 40 mg every other week seemed to produce better results than 80 mg); however, the best results once again were achieved when treatment was combined with methotrexate (MTX low-dose, average 16 mg/week). The side effects appeared to be less severe with adalimumab than other available monoclonal antibodies; however, further comparisons will be necessary. The study seems to demonstrate that MTX is less effective alone than in combination with adalimumab in long-lasting RA. However, given its complex role as an antiproliferative/antiinflammatory agent, MTX remains the fundamental "gold standard" for RA treatment, although other agents such as leflunomide (LFN) (or even cyclophosphamide) may play a similar role (1).*

The main question that now arises is: "When is the best time during the course of RA to add the TNFα blockade to the antiproliferative/antiinflammatory agent (and to the frequently associated low-dose prednisolone)?" Various treatment algorithms have recently been proposed (2).

Since TNFα is one of the earliest and most active mediators of RAsynovitis and since articular damage starts soon in the disease course, it would now appear sensible to consider early intervention with TNFα blockade (3). Of course, both antiproliferative/antiinflammatory agents (MTX or LFN) and prednisone also act as anti-TNFα agents since they start the blockade at the level of inflammatory cell production, but their action may be better sustained by the concomitant directly targeted effect of true TNFα blockers (i.e. adalimumab) (4).

The second problem is for how long and with what frequency the RA patient should be treated with the TNFα blocker (apart from such obvious considerations as the well-known differing half-lives of etanercept and infliximab). It is evident that the combination of different drugs such as MTX and prednisolone, plus TNFα blockers, after some time will reduce the body fluid concentrations of TNFα from the levels seen at the beginning of therapy, as well as the activity of the primary TNFα-producing cells (monocytes and macrophages). During this period severe side effects linked to the excessive perturbation of TNFα synthesis might arise and the frequency of the dosage should be reduced. In addition, neither TNFα nor IL-1 blockade will resolve the disease progression in all RA patients and new combination strategies will still be needed (5). Keeping these caveats in mind, adalimumab seems now ready to play a key role in RA treatment.

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