Dose-loading with hydroxychloroquine is effective in early and active rheumatoid arthritis

Authors: D.E. Furst et al.
Title: Dose-loading with hydroxychloroquine improves the rate of response in early active rheumatoid arthritis

Aim: Hydroxychloroquine (HCQ) requires 3 - 6 months to become effective in rheumatoid arthritis (RA). To overcome its slow onset of action, patients could be "dose-loaded" with HCQ over a short period of time to increase the amount of the drug in the tissues and to quickly reach a steady-state level, with the dosage being later reduced to maintenance levels. To test this hypothesis a 24-week study investigated the effectiveness of HCQ dose-loading in increasing the percentage of responders or the rate of response in RA.

Methods: 212 RA patients (pts) were asked to discontinue non-steroidal anti-inflammatory drug (NSAID) treatment and were stabilised with 1,000 mg naproxen/day for 4 weeks (phase 1). Then a 6-week double-blind, multi-center trial was conducted to compare treatment with HCQ at 400 mg/day (71 pts), 800 mg/day (71 pts), and 1200 mg/day (66 pts) (phase 2), followed by 18 weeks of open-label HCQ treatment at 400 mg/day (phase 3).

Inclusion criteria were: active disease, disease flare within 2 weeks of withdrawal of baseline NSAIDs, sulfasalazine and/or auranofin discontinued at least 2 months prior to study entry, and HCQ (if previously taken) not used for at least 2 months. Prednisone was allowed if the dosage did not exceed 10 mg/day for at least one month prior to study entry, and the dosage had to remain stable during the study. RA patients who had taken disease modifying drugs other than sulfasalazine and/or auranofin, or intrarticular or intramuscular steroids in the previous month, were excluded.

Every patient was evaluated weekly for efficacy and toxicity during phase 2, and at 8, 10, 14 and 24 weeks during phase 3. At each of the 14 visits, the following data were assessed: tender and swollen joint counts, duration of morning stiffness, global assessment of overall disease activity by the physician and the patient using a 10 cm visual analogue scale (VAS), the patient’s evaluation of pain at the time of the visit on a 10 cm VAS. Some of these items were drawn from the modified Paulus criteria, a combined index of response used to compare treatment regimens, in which the patient must show improvement in 4 out of 6 criteria, as follows: 20% improvement in the tender or the swollen joint count, ESR, or morning stiffness, and/or at least a 2-grade change (out of 5) in the patient’s or physician’s assessment of global disease activity. The modified Health Assessment Questionnaire (M-HAQ), the cost of illness questionnaire, and the Quality of Well-Being Assessment (by telephone contact) were administered at the beginning of the double-blind phase, after 6 weeks and after 24 weeks. Also evaluated were rheumatoid factor, C-reactive protein (tested at weeks 0, 6 and 24), and ESR (at screening and at weeks 0, 2, 4, 6, 10 and 24). A complete eye check-up, and routine hematologic and urinary tests were performed at baseline and at weeks 0, 2, 4, 6, 10, and 24.

Descriptive statistical analysis was carried out on all the continuous variables. Efficacy parameters were examined at baseline, and then weekly through week 6, and at weeks 8, 10, 14, 18 and 24 using repeated analysis of variance (ANOVA). Analysis of covariance was applied to the single variables. Subgroup analysis was performed using an ANOVA with factors for treatment, investigator site, and the interaction of the two.

Results: All patients had mild, active disease at the beginning of HCQ treatment; 31 - 43% were rheumatoid factor positive, with no previous DMARD use and a mean swollen joint count of 8.6 - 10.4. The drop-out rate due to side effects was dose-related (4.1%, 7.0% and 9% in the 400, 800 and 1200 mg/day groups, respectively). In all, 57 patients completed the 400 mg/day regimen, 56 completed the 800 mg/day regimen, and 50 completed the 1200 mg/day regimen.

During phase 2, there were no statistically significant differences between the 3 groups in the individual efficacy measures, although the greatest improvement was seen in the 1,200 mg/day regimen during phase 2 of the study was maintained in phase 3 (open label), while the groups receiving the lower doses caught up over time. At week 24 the differences in response according to the Paulus criteria were not significantly different (P = 0.352) and there were no statistically significant differences among the three groups for any of the individual efficacy measures.

Study discontinuations due to adverse events were dose-related (3, 5 and 6 patients respectively from the 400 mg/day, 800 mg/day, and 1200 mg/day groups). The most common side effects involved the gastrointestinal system; nausea and vomiting during phase 2 were significantly more frequent in the 800 mg/day and 1200 mg/day groups than in the 400 mg/day group (P = 0.352). Ocular abnormalities occurred in 17 patients (8%) and were not dose-related.

Conclusions: Dose-loading with 1,200 mg/day of HCQ can significantly accelerate the onset of action of HCQ, improving the response rate over 6 weeks in early RA patients with no significant increase in toxicity. This suggests that the use of the HCQ dose-loading strategy could be a very useful tool to control early RA. It should be noted that the initial dose-loading must be followed by a maintenance dose in order to maintain the effectiveness of the drug.
Comment

There is much interest in improving the speed of response to DMARDs. This is consequent on the evidence that untreated inflammation is damaging and that inflammation is often maximal at an early untreated stage of disease. Hydroxychloroquine is a drug with a relatively low side-effect profile, but its use is limited by its slow speed of onset (up to 6 months) and its relatively mild efficacy.

The current study examined the use of an induction regime of 6 weeks high dose hydroxychloroquine in patients who had a flare induced by reducing their current therapy. The initial response rate was increased (but not significantly) after the first six weeks and on reverting to a standard dose the lower dose caught up in response. However, there was a dose-dependent significant increase in gastrointestinal toxicity.

The major issue in rheumatology is toxicity versus efficacy. The importance of toxicity is that once a patient has ceased a particular medication they probably will never again take this drug. In a life-long disease this is an important consideration. Therefore, from a clinical viewpoint the question arises as to whether one can justify the non-significant increase in efficacy when there is an associated increase in toxicity. Perhaps an alternative approach would be justified, such as giving corticosteroids (intra-articularly or intra-muscularly) which produces a rapid response without the loss to patients through toxicity. Such an alternative ought to now be tested in an effectiveness situation. This study does nevertheless represent an interesting approach which may have application in individual patients.

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