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Hydroxychloroquine effectiveness in reducing symptoms of hand osteoarthritis: a Randomized Trial

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Abstract

Background: It is thought that synovitis may play a role in producing symptoms in people with hand osteoarthritis (OA), but data on slow-acting anti-inflammatory treatments are sparse.

Objective: To determine the effectiveness of hydroxychloroquine versus placebo as an analgesic treatment for hand OA.

Design: Randomized, double-blind, placebo-controlled clinical trial with 12-month follow-up.

Setting: 13 primary- and secondary-care centres in England.

Participants: Of 316 patients screened, 248 participants (82% women, mean age 62.7 years) with symptomatic (VAS pain ≥4/10) and radiographic hand OA were randomized. 210 (84.7%) completed the 6-month primary endpoint.

Intervention: Hydroxychloroquine (200-400mg) or placebo (1:1) for 12 months in addition to ongoing usual care.

Measurements: The primary endpoint was average hand pain during the previous 2 weeks (numerical rating scale [0-10], NRS) at 6-months. Secondary endpoints included self-reported pain and function, grip strength, quality-of-life, radiographic structural change and adverse events. Baseline ultrasonography was performed.

Results: At 6 months, the mean hand pain (as measured by NRS) was 5.49 and 5.66 in the placebo and hydroxychloroquine groups, with a treatment difference of -0.16 points (95% CI: -0.73 to 0.40, p=0.57). Results were robust to adjustments for adherence, missing data and use of rescue medication. There were no significant treatment differences at 3, 6 or 12-

months for any secondary outcomes. On ultrasound, 94% (133/143) had ≥1 joint positive for greyscale synovitis, 59% were Power Doppler positive. Baseline structural damage or synovitis did not affect treatment response. Fifteen serious adverse events were reported (hydroxychloroquine: 7 [3 defined as possibly related], placebo: 8).

Limitations: Hydroxychloroquine dosage restrictions may have reduced efficacy.

Conclusions: Hydroxychloroquine was no more effective than placebo for pain relief in people with moderate to severe hand pain and radiographic OA.

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Symptomatic hand osteoarthritis (OA) affects 4-31% of adults over the age of 70, and 3-15% over the age of 60 (1-7). Individuals report chronic persistent pain and considerable difficulty with daily activities (8). However there are few effective therapies for this condition and use of these therapies is often limited by patients' comorbidities or toxicities (9-11). Consequently primary and secondary care physicians seek alternative options to improve quality of life for people with this painful, disabling disease. Anecdotal reports suggest hydroxychloroquine (HCQ) is one such therapy. It has been used as an unlicensed treatment in many countries when other options have failed, mainly for the subset of patients with "inflammatory" hand OA (12,13). HCQ is an established drug treatment for inflammatory arthritides such as rheumatoid arthritis (RA), supported by placebo-controlled trials demonstrating its efficacy, as a monotherapy and in combination with other RA drugs, and acceptable safety profile (14,15). With increasing evidence that inflammation is highly prevalent in OA and may have a role in symptoms (16-20) and three small pilot studies suggesting reduction in hand pain with HCQ (21-23), there is a rationale for exploring the efficacy of HCQ as a treatment for hand OA.

The objective of the Hydroxychloroquine Effectiveness in Reducing symptoms of hand Osteoarthritis (HERO) Trial was to test the hypothesis that HCQ is an effective symptomatic treatment when used in people with at least moderate symptomatic hand OA and inadequate response to current therapies including NSAIDs and opioids.

Methods

Design Overview

The HERO trial was an investigator-led, pragmatic, multi-centre, superiority, randomized, 1:1 placebo-controlled trial. The research protocol (Appendix 1) was approved by Leeds East Research Ethics Committee (12/YH/0151), the UK Medicines and Health Regulatory Authority (MHRA) and registered on ISRCTN (ISRCTN91859104) in parallel. Participants were recruited from September 24th 2012 until May 27th 2014, with participants followed-up for 12-months post-randomization (follow-up completed April 25th 2015). Written informed consent was obtained for all participants prior to screening. One participant was recruited (24.09.2012) prior to protocol registration (17.10.2012), however no changes were made to the protocol between these time-points and therefore this participant is similar to all other trial participants. Full trial design details are available (Appendices 1-4).

Setting and Participants

The trial involved 13 National Health Service (NHS) hospitals in England, with recruitment taking place through primary care and secondary care-based musculoskeletal clinics. Patients were eligible if aged ≥18 with self-reported, inadequate response or side-effects to existing medication (including paracetamol, oral NSAID or opioid); moderately severe symptoms (hand pain ≥4/10 on a 0-10 visual analogue scale) for more than half of days in the last 3 months; fulfilled American College of Rheumatology criteria for OA (24); hand radiographs in the past 5 years with changes consistent with OA; stable, no change to or no use of analgesics (including NSAIDs) for at least 4 weeks or glucosamine or chondroitin for at least 4 months; and capable and willing to give consent and adhere to the study protocol. Exclusion criteria were inflammatory arthritis; psoriasis; CMC joint (CMCJ) involvement only or predominant CMCJ pain; oral, intramuscular, intra-articular, intravenous steroids or other anti-synovial agents or any new hand OA therapies during the last two months; intra-articular hyaluronans in last 6 months; uncontrolled disease states where flares are commonly treated with corticosteroids; serious uncontrolled medical condition; unexplained visual

impairment; pregnant or lactating; melanoma or non-skin cancer in the past 3 years, significant haematological or biochemical abnormality (Appendix 4). Rheumatoid factor (RF) and anti-CCP were measured in all eligible participants to exclude inflammatory arthritis.

Randomization and Interventions

Patients were randomized to either hydroxychloroquine (200, 300 or 400mg, with dosage calculated according to ideal body weight to give a maximum dose of 6.5mg/kg/day) or placebo. Randomization (1:1) was computer-generated (PRISYM ClinTrial) in advance by the contract manufacturer using random permuted blocks, without stratification. The contract manufacturer prepared trial drug with over-encapsulation to create identical intervention and placebo-control products with no involvement from the research team, and assigned intervention and control drug packs in sequence to recruiting sites. All parties remained blind to treatment allocation throughout the trial. Adverse events, vital signs and blood monitoring were assessed on an ongoing basis during follow-up. All elements of participant care were left to the discretion of the site research team in line with the pragmatic nature of the HERO trial, with the exception that steroids and new or experimental interventions were not permitted during follow-up. Adherence to trial medication was collected using multiple methods to provide an estimate of compliance, including site-reported non-adherence, participant-reported Brief Medication Questionnaire (25), and pharmacy records of returned medication. Quality of adherence data was reviewed prior to unblinding to determine non-adherence criteria for analysis (Appendix 4). Participants were asked about adverse events (AEs) at all visits and these were reviewed by a physician for severity, duration and relatedness to investigational medicinal product (IMP). SAEs were defined according to pre-specified criteria, as detailed in the protocol (Appendix 1), assessed for causality and expectedness by a physician and reported within 24 hours.

Outcomes and Follow-up

Data collection was completed using standardized case report forms at screening, baseline,

3, 6 and 12-months. The primary outcome was overall hand pain severity over the past 2 weeks, measured on an 11-point (0-10) Numerical Rating Scale (NRS), at 6-months follow-up (26). This outcome was also assessed at baseline, 3 and 12-months. Secondary outcomes included: pain severity in the most painful joint (NRS over last 2 weeks), AUSCAN pain and function scales (27), grip strength (measured using a dynamometer) (28), structural damage using bilateral hand radiograph data (29), Osteoarthritis Quality of Life (OAQoL) (30), and Short-form 12 (SF-12) Physical and Mental Component Score (31). Bilateral hand radiographs (baseline, 12-months) were captured according to a standardized protocol (Appendix 4) and scored in pairs at the end of the study by a musculoskeletal radiologist who was blinded to participant identity and treatment allocation. Baseline ultrasound imaging was performed for the dominant hand of all participants enrolled at the six ultrasound sub-study centres using a standardised protocol (Appendix 4) and following a group training day for the ultrasound operators.

A full list of secondary outcomes is described in Appendix 4 and Appendix Table 1. Cost-effectiveness data, collected at baseline and 12-months, will be presented in a separate publication.

Statistical Analysis

The HERO trial was powered to detect a standard effect size of 0.4, equivalent to the reported effect size of NSAIDs as a treatment for hand OA (32,33) and a reduction in pain of 0.8 score points (or 15%) on the NRS (32,33) which lies within the minimal clinically important difference for change in pain in a randomized trial (10/20%)(34). To detect a standard effect size of 0.4 with 80% power and 5% two-sided significance, 99 patients were required per arm. Allowing for 20% dropout and equal numbers per centre, the total target sample size was 252 patients.

The analyses followed a pre-specified statistical analysis plan, endorsed by the data and safety monitoring committee, and were performed using Stata version 13 (StataCorp, Texas, USA). The statistician remained blinded to treatment allocation until verification of the primary analysis. The primary analysis was intention-to-treat (ITT), analysing participants in their randomization group. A linear mixed effects model was used to analyse overall hand pain NRS over time. The model assumed an exchangeable covariance structure to account for the repeated measures over time, and included fixed effects of time (3, 6, 12-months), treatment group, time-by-treatment interaction, and the pre-specified covariates (baseline hand pain severity, average grip strength, concomitant analgesic use, age, gender and BMI). The model estimate of group differences at 6-months constituted the primary endpoint of the trial. As the mixed-effects analysis model incorporated follow-up data from all available time-points simultaneously, participants with valid outcome data at one or more follow-up visits and complete baseline covariate data were included. Secondary analyses explored robustness to adjustments based on treatment adherence up to 6-months (binary, based on self-reported non-adherence, treatment withdrawals and receipt of corticosteroids; analysis using complier-average causal effect (CACE); implemented using instrumental variable analysis (35)), 'missingness' (using multiple imputation by chained equations) and receipt of rescue medication during follow-up (increased dose or addition of any NSAIDs, opioids or paracetamol or steroid injection to the hand, added as a time varying covariate (36)), all detailed further in Appendix 4. The primary analysis was repeated for participants with OA confirmed by imaging. To account for deviations between intended and achieved follow-up timing, predicted effects at 3, 6, and 12-months were obtained from a mixed effects model, including time of response since randomization as a continuous variable with a random slope.

Planned sub-group analyses explored differences in treatment response for different levels of structural damage (mild/moderate versus severe damage based on Kallman score tertiles) and treatment differences in the presence/absence of ultrasound synovitis (assessed by

greyscale, Power Doppler and total synovitis) and osteophytes. Analyses were conducted by adding an interaction term between treatment allocation and the sub-groups to the primary analysis model. In the interest of planning future research, effectiveness was explored across four further sub-groups that were hypothesised to affect the treatment mechanism of HCQ, specifically average grip strength (low (<30lbs) and high strength (≥30lbs) based on median strength at baseline) and presence/absence of thumb pain.

Due to the large number of secondary outcomes, only outcomes of primary clinical interest were analysed using mixed-effects models, giving treatment effect estimates and p-values at each follow-up point. The remaining secondary outcomes were reported descriptively only.

Role of the funding source

HERO was funded by an Arthritis Research UK Clinical Studies Grant (Reference 19545). Arthritis Research UK were not involved in the study design, conduct, analysis, data interpretation, manuscript preparation or decision to submit the manuscript for publication.

Results

Of 316 patients screened, the HERO trial recruited 248 participants (74.5%, 124 in each trial arm) with hand OA from 13 centres in England, while 68 patients were excluded (Appendix Figure 1). Baseline characteristics (Table 1) were balanced across treatment arms. Participants were on average 62.7 years old (SD=9.1), 81.9% women, predominantly of Caucasian ethnicity and had been suffering with hand pain for a median of 5 years. Nearly all participants (89.9%) were taking analgesic medication for their hand OA, and median hand pain over the past two weeks was 7 points on the 0 to 10 NRS. Five participants had raised Rheumatoid Factor (RF) and one had raised anti-cyclic citrullinated peptide (CCP). In all six cases this was determined to be non-clinically significant by the site PI and not indicative of inflammatory arthritis.

Most participants (70.6%) were prescribed a 300 mg daily dose of investigational medicinal product (IMP, HCQ: 85, placebo: 90, Appendix Table 2), with all but one participant remaining on the same dose throughout the trial. Balance in participant characteristics was maintained for patients included in the intention-to-treat analysis. In total, 45 participants (18.1%, HCQ: 24, placebo: 21) were non-adherent to the treatment, which is likely to be a conservative estimate, assuming unknown, unreported non-adherence. Non-adherers tended to be slightly younger (mean of 61.2 years versus 63.0 years) with greater average grip strength (36.1lbs versus 31.3lbs). Follow-up was 84.7% at 6-months and 76.6% at 12-months. A total of 134 participants (54.0%) received rescue medication during the trial (HCQ: 63, placebo: 71).

Primary Outcome

Hand pain severity improved for participants with observed data in both arms by around 1 point between baseline and 3 months, and this was maintained up to 12-months (Figure 1A). Outcome data was not available for 20 patients at 3-months, 38 patients at 6-months and 58 patients at 12-months follow-up (Appendix Figure 1). A total of 232 participants (93.5%, HCQ: 113, placebo:119) were included in the primary intention-to-treat analysis. Differences in hand pain severity between treatment groups were small at each follow-up and not statistically significant (Table 2; Figure 1A). At the 6-month primary endpoint, the treatment difference estimate was -0.16 points on the NRS pain scale (95% CI: -0.73 to 0.40, p=0.57), i.e. participants in the HCQ arm reported worse pain by 0.16 score points, equivalent to a standard effect size of 0.07. The confidence interval excludes a clinically meaningful difference in improvement of 0.8 scale points, on which the trial was powered. Improvements of this magnitude or greater were reported for 58 of 107 patients in the HCQ group and 59 of 103 patients in the placebo group with NRS pain score reported at 6-months.

Results were robust to secondary analyses of hand pain severity. When non-adherence was accounted for, the treatment effect became positive (0.21 scale points in favour of HCQ). While the 95% confidence interval remained wide (-0.44 to 0.86), the upper limit did include the potentially meaningful clinical difference of 0.8 scale points (Table 2). When multiple imputation was used to address missing outcome and baseline grip strength data, results were comparable with the primary analysis of hand pain severity with similar confidence interval widths (Table 2). Treatment effects of the analysis accounting for rescue medication closely resembled those of the primary analysis of hand pain severity (Table 2). A repeat analysis for participants with confirmed OA on imaging (n=171 of 182 with available imaging data and analysis covariates) as well as estimates treating response time continuously revealed no significant treatment differences (Appendix Table 3), with confidence intervals excluding a clinically meaningful difference.

Safety

A total of 15 serious adverse events (SAEs) were reported by 15 patients (HCQ: 7, placebo: 8; Appendix Table 5). No deaths were reported. Of the 15 SAEs, three were assessed as being related to HCQ: prolonged QT interval with ventricular arrhythmias, erythema multiforme and acute generalised erythematous pustulosis.

Secondary Outcomes, Subgroup Analyses and Ultrasound Findings

Hand pain and most self-reported symptom outcomes improved in the short term in both arms and then plateaued over follow-up. Mental functioning outcomes, grip strength and structural damage remained unchanged. There were no systematic treatment differences between HCQ and placebo for any of the secondary outcomes (Table 3, Appendix Table 4). A difference of borderline statistical significance (SF-12 physical component score at 12 months (p=0.053)) could be spurious in light of the number of outcomes and timepoints assessed.

Radiograph data at baseline, recorded as Kallman scores, were available for 188 participants (75.8%), 94 in each arm. Data tertiles were used to group observations into mild to moderate damage (score 0-57) and severe damage (score 58-113). There were no substantial differences between severity groups in response to treatment, and the value of a group by treatment interaction term added to the primary analysis model was not statistically significant (p=0.25; Figure 1B). A significant interaction term with treatment allocation (p=0.033) indicated that participants with greater grip strength may benefit more from HCQ treatment than weaker participants (Appendix Figure 2). A treatment interaction with baseline thumb pain did not reveal meaningful group differences (p=0.136, Appendix Figure 3). As the latter two analyses were exploratory, results may be considered spurious.

Baseline ultrasound images were taken for a subset of randomized participants (n=143, 57.7%; HCQ: 74, placebo: 67). The vast majority were positive for synovitis assessed by greyscale (93.7%) and over half for synovitis assessed by Power Doppler (58.7%). Osteophytes were present in at least one joint for all participants. There were no significant treatment differences between participants with positive or negative Power Doppler status (p=0.85 for the interaction term with treatment, Figure 1C). Meaningful sub-group analyses were not possible for greyscale synovitis (only nine negative cases), total synovitis (Power Doppler did not add new cases) or osteophytes.

Conclusions

The HERO trial was designed as a pragmatic trial with a view to replicating anecdotal reports of HCQ use in clinical practice, and powered to detect a moderate effect equivalent to that for NSAIDs in this population. We found that HCQ was not a more effective analgesic than placebo when added to usual care in people with moderate to severe hand OA. There were no demographic differences in the patient population that might explain the lack of efficacy. Background analgesic use did not differ between groups and baseline inflammation and structural damage did not affect response to HCQ. The study therefore presents no evidence

to suggest that HCQ should be considered within the management plan of people with hand OA.

In terms of age, gender distribution and BMI, our population reflects that observed in recent community-based cohorts of hand OA in the UK and Europe (37-40). We deliberately excluded participants with isolated 1st carpometacarpal joint (CMCJ) involvement or predominant 1st CMCJ pain, due to the potential differences in mechanism of disease between 1st CMCJ and distal and proximal interphalangeal joint OA. Whilst just over half of participants had concomitant thumb pain, in line with previous community studies (37-40), this was not the primary site of their hand pain and no difference in treatment effect was observed in those with or without CMCJ involvement. Consistent with recent imaging studies, ultrasound-detected greyscale synovitis was common, with nearly all participants having moderate grade synovitis in at least one joint. Power Doppler synovitis although less common, present in just over half of participants, was not associated with treatment differences. Based on the additional sub-group analyses, weaker grip strength may predispose people to tenosynovitis or enthesitis, alternative causes for hand pain in this population. This suggests a need to consider grip strength in this population when planning further studies.

A growing body of imaging and experimental evidence suggests a role for synovitis in the pathogenesis of OA and an association with pain. Ultrasound-detected synovitis is independently associated with radiographic progression of hand OA, painful hand joints are associated with the presence of ultrasound- and MRI-detected synovitis, and response to intramuscular steroids (thought to work by reducing synovitis) in hand OA is associated with higher levels of baseline ultrasound-detected synovitis (19,41-44). However, in the HERO study baseline synovitis was not linked to treatment effect. Our inclusion criteria may have resulted in participants where the level and/or type of inflammation was not severe: a previous study has suggested that early OA may be more inflammatory than established OA,

and that molecular pathways driving inflammation may change as the disease progresses (45). By selecting participants with moderate to severe hand OA, established radiographic changes and inadequate response to existing therapies, we may have missed an early window of opportunity for HCQ to have therapeutic benefit.

Hydroxychloroquine has various known immunomodulatory effects, and although established as a treatment option in the management of inflammatory arthritides, its specific mechanism of action remains unclear. In RA, therapeutic activity has been linked to modulation of antigen-processing activity, including inhibition of T-cell activation and cytokine release (46,47); increasing evidence of involvement of these pathways in inflammation and cartilage degeneration in OA (48-50) supported HCQ as a potential OA therapy. More recent data implicates intracellular toll-like receptors (TLR), in particular TLR-9, as key mediators of HCQ's anti-inflammatory properties, in line with growing evidence of the role of the innate immune system in rheumatic disease. Although limited evidence suggests that the innate immune system may be important in OA pathogenesis (51), for example increased TLR expression in OA tissue (52-55), this work is still in its infancy. Further understanding of these mechanisms in OA may enable stratification according to a defined inflammatory phenotype.

Other potential limitations to the study include restriction of HCQ dosing to the British National Formulary recommended maximum dose of 6.5 mg/kg/day (56), with the majority of patients taking 300 mg daily. In clinical RA practice, patients may commence HCQ at a higher dose (400 mg), with reduction to a lower maintenance dose after 3-6 months. However, only 5.6% of the HCQ group were on the lowest dose of 200mg and no dose-response relationship with treatment effect was observed. The co-occurrence of MRI-detected bone marrow lesions (BMLs) with hand synovitis has been found to worsen pain and, as demonstrated in knee OA, may contribute to pain (57,58). Since BMLs cannot be detected by ultrasound or x-ray, we were unable to examine BMLs in this study. The failure

of HCQ as an analgesic in this study may reflect the mild anti-inflammatory activity of HCQ, suboptimal dosing, or that the level and/or type of inflammation in our population did not match the mechanism of HCQ. However it is also worth considering, in light of the current result and the previous failure of biologic DMARDs, that simply treating 'macroscopic' or imaging-detected synovitis with DMARDs is not a useful analgesic strategy. Further exploration of the molecular mechanisms of inflammation in OA may provide targets and better patient phenotyping may enable exclusion of other causes of hand pain such as tenosynovitis.

In summary, HCQ was not more effective than placebo in reducing symptoms or radiographic progression in people selected for moderate to severe hand pain and radiographic OA. Our findings in this full-scale pragmatic trial do not support the current practice for the off-label use of Hydroxychloroquine in those with hand osteoarthritis.

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References

1. Zhang Y, Niu J, Kelly-Hayes M, Chaisson CE, Aliabadi P, Felson DT. Prevalence of symptomatic hand osteoarthritis and its impact on functional status among the elderly: The Framingham Study. Am J Epidemiol. 2002;156(11):1021-7.
2. Zhang Y, Xu L, Nevitt MC, Niu J, Goggins JP, Aliabadi P, et al. Lower prevalence of hand osteoarthritis among Chinese subjects in Beijing compared with white subjects in the United States: the Beijing Osteoarthritis Study. Arthritis Rheum. 2003;48(4):1034-40.
3. Dillon CF, Hirsch R, Rasch EK, Gu Q. Symptomatic hand osteoarthritis in the United States: prevalence and functional impairment estimates from the third U.S. National Health and Nutrition Examination Survey, 1991-1994. Am J Phys Med Rehabil. 2007;86(1):12-21.
4. Andrianakos AA, Kontelis LK, Karamitsos DG, Aslanidis SI, Georgountzos AI, Kaziolas GO, et al. Prevalence of symptomatic knee, hand, and hip osteoarthritis in Greece. The ESORDIG study. J Rheumatol. 2006;33(12):2507-13.
5. Carmona L, Ballina J, Gabriel R, Laffon A, Group ES. The burden of musculoskeletal diseases in the general population of Spain: results from a national survey. Ann Rheum Dis. 2001;60(11):1040-5.
6. Grotle M, Hagen KB, Natvig B, Dahl FA, Kvien TK. Prevalence and burden of osteoarthritis: results from a population survey in Norway. J Rheumatol. 2008;35(4):677-84.
7. Mannoni A, Briganti MP, Di Bari M, Ferrucci L, Costanzo S, Serni U, et al. Epidemiological profile of symptomatic osteoarthritis in older adults: a population based study in Dicomano, Italy. Ann Rheum Dis. 2003;62(6):576-8.

8. Dziedzic K, Thomas E, Hill S, Wilkie R, Peat G, Croft PR**.** The impact of musculoskeletal hand problems in older adults: findings from the North Staffordshire Osteoarthritis Project (NorStOP). Rheumatology. 2007;46(6):963-7.

9. Machado GC, Maher CG, Ferreira PH, Pinheiro MB, Lin CW, Day RO, et al. Efficacy and safety of paracetamol for spinal pain and osteoarthritis: systematic review and meta-analysis of randomised placebo controlled trials. BMJ. 2015;350:h1225.

10. Machado GC, Maher CG, Ferreira PH, Day RO, Pinheiro MB, Ferreira ML**.** Non-steroidal anti-inflammatory drugs for spinal pain: a systematic review and meta-analysis. Ann Rheum Dis. 2017;76(7):1269-1278.

11. Hochberg MC, Altman RD, April KT, Benkhalti M, Guyatt G, McGowan J, et al. American College of Rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee. Arthritis Care Res (Hoboken). 2012;64(4):465-74.

12. Punzi L, Frigato M, Frallonardo P, Ramonda R**.** Inflammatory osteoarthritis of the hand. Best Pract Res Clin Rheumatol. 2010;24(3):301-12.

13. Ehrlick GE**.** Erosive inflammatory and primary generalized osteoarthritis. Osteoarthritis 3rd ed. Philadelphia: W.B. Saunders 2001.

14. Haar D, Solvkjaer M, Unger B, Rasmussen KJ, Christensen L, Hansen TM**.** A double-blind comparative study of hydroxychloroquine and dapsone, alone and in combination, in rheumatoid arthritis. Scand J Rheumatol. 1993;22(3):113-8.

15. Clark P, Casas E, Tugwell P, Medina C, Gheno C, Tenorio G, et al. Hydroxychloroquine compared with placebo in rheumatoid arthritis. A randomized controlled trial. Annals of internal medicine. 1993;119(11):1067-71.

16. Samuels J, Krasnokutsky S, Abramson SB**.** Osteoarthritis: a tale of three tissues. Bull NYU Hosp Jt Dis. 2008;66(3):244-50.

17. Krasnokutsky S, Attur M, Palmer G, Samuels J, Abramson SB. Current concepts in the pathogenesis of osteoarthritis. Osteoarthritis Cartilage. 2008;16 Suppl 3:S1-3.

18. Keen HI, Wakefield RJ, Grainger AJ, Hensor EM, Emery P, Conaghan PG. An ultrasonographic study of osteoarthritis of the hand: synovitis and its relationship to structural pathology and symptoms. Arthritis Rheum. 2008;59(12):1756-63.

19. Keen HI, Wakefield RJ, Hensor EM, Emery P, Conaghan PG. Response of symptoms and synovitis to intra-muscular methylprednisolone in osteoarthritis of the hand: an ultrasonographic study. Rheumatology (Oxford). 2010;49(6):1093-100.

20. Vlychou M, Koutroumpas A, Malizos K, Sakkas LI. Ultrasonographic evidence of inflammation is frequent in hands of patients with erosive osteoarthritis. Osteoarthritis Cartilage. 2009;17(10):1283-7.

21. Bryant LR, des Rosier KF, Carpenter MT. Hydroxychloroquine in the treatment of erosive osteoarthritis. J Rheumatol. 1995;22(8):1527-31.

22. Punzi L, Bertazzolo N, Pianon M, Michelotto M, Todesco S. Soluble interleukin 2 receptors and treatment with hydroxychloroquine in erosive osteoarthritis. J Rheumatol. 1996;23(8):1477-8.

23. Robertson CR, Rice JR, Allen NB. Treatment of erosive osteoarthritis with hydroxychloroquine. Arthritis Rheum. 1993;36(Suppl):S167.

24. Altman R, Alarcon G, Appelrouth D, Bloch D, Borenstein D, Brandt K, et al. The American College of Rheumatology criteria for the classification and reporting of osteoarthritis of the hand. Arthritis Rheum. 1990;33(11):1601-10.

25. Vitolins MZ, Rand CS, Rapp SR, Ribisl PM, Sevick MA. Measuring adherence to behavioral and medical interventions. Controlled Clinical Trials. 2000;21(5 Suppl):188S-94S.

26. Chang L. A Psychometric Evaluation of 4-Point and 6-Point Likert-Type Scales in Relation to Reliability and Validity. Applied Psychological Measurements. 1994;18(3):205-15.

27. Bellamy N, Campbell J, Haraoui B, Gerecz-Simon E, Buchbinder R, Hobby K, et al. Clinimetric properties of the AUSCAN Osteoarthritis Hand Index: an evaluation of reliability, validity and responsiveness. Osteoarthritis Cartilage. 2002;10(11):863-9.

28. Mathiowetz V, Weber K, Volland G, Kashman N**.** Reliability and validity of grip and pinch strength evaluations. J Hand Surg Am. 1984;9(2):222-6.

29. Kallman DA, Wigley FM, Scott WW, Jr., Hochberg MC, Tobin JD**.** New radiographic grading scales for osteoarthritis of the hand. Reliability for determining prevalence and progression. Arthritis Rheum. 1989;32(12):1584-91.

30. Keenan AM, McKenna SP, Doward LC, Conaghan PG, Emery P, Tennant A**.** Development and validation of a needs-based quality of life instrument for osteoarthritis. Arthritis Rheum. 2008;59(6):841-8.

31. Ware J, Jr., Kosinski M, Keller SD**.** A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. Med Care. 1996;34(3):220-33.

32. Myers H, Nicholls E, Handy J, Peat G, Thomas E, Duncan R, et al. The Clinical Assessment Study of the Hand (CAS-HA): a prospective study of musculoskeletal hand problems in the general population. BMC MSK Dis. 2007;8:85.

33. Dziedzic KS, Hill S, Nicholls E, Hammond A, Myers H, Whitehurst T, et al. Self management, joint protection and exercises in hand osteoarthritis: a randomised controlled trial with cost effectiveness analyses. BMC MSK Dis. 2011;12:156.

34. Dworkin RH, Turk DC, Wyrwich KW, Beaton D, Cleeland CS, Farrar JT, et al. Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations. J Pain. 2008;9(2):105-21.

35. Angrist JD, Imbens GW, Rubin DB**.** Identification of causal effects using instrumental variables. JASA. 1996;91(434):444-55.

36. White IR, Bamias C, Hardy P, Pocock S, Warner J. Randomized clinical trials with added rescue medication: some approaches to their analysis and interpretation. Stat Med. 2001;20(20):2995-3008.

37. Marshall M, Peat G, Nicholls E, van der Windt D, Myers H, Dziedzic K**.** Subsets of symptomatic hand osteoarthritis in community-dwelling older adults in the United Kingdom: prevalence, inter-relationships, risk factor profiles and clinical characteristics at baseline and 3-years. Osteoarthritis Cartilage. 2013;21(11):1674-84.

38. Castano Carou A, Pita Fernandez S, Pertega Diaz S, de Toro Santos FJ, Grupo de estudio E**.** Clinical profile, level of affection and therapeutic management of patients with osteoarthritis in primary care: The Spanish multicenter study EVALUA. Reumatol Clin. 2015;11(6):353-60.

39. Siviero P, Zambon S, Limongi F, Castell MV, Cooper C, Deeg DJ, et al. How Hand Osteoarthritis, Comorbidity, and Pain Interact to Determine Functional Limitation in Older People: Observations From the European Project on OSteoArthritis Study. Arthritis Rheumatol. 2016;68(11):2662-70.

40. Bellamy N, Campbell J, Haraoui B, Buchbinder R, Hobby K, Roth JH, et al. Dimensionality and clinical importance of pain and disability in hand osteoarthritis: Development of the Australian/Canadian (AUSCAN) Osteoarthritis Hand Index. Osteoarthritis Cartilage. 2002;10(11):855-62.

41. Haugen IK, Boyesen P, Slatkowsky-Christensen B, Sesseng S, van der Heijde D, Kvien TK**.** Associations between MRI-defined synovitis, bone marrow lesions and structural features and measures of pain and physical function in hand osteoarthritis. Ann Rheum Dis. 2012;71(6):899-904.

42. Kortekaas MC, Kwok WY, Reijnierse M, Kloppenburg M. Inflammatory ultrasound features show independent associations with progression of structural damage after over 2 years of follow-up in patients with hand osteoarthritis. Ann Rheum Dis. 2015;74(9):1720-4.
43. Kortekaas MC, Kwok WY, Reijnierse M, Huizinga TW, Kloppenburg M. Follow-up study of inflammatory ultrasound features in hand osteoarthritis over a period of 3 months: variable as well as constant. Osteoarthritis Cartilage. 2014;22(1):40-3.
44. Mancarella L, Addimanda O, Cavallari C, Meliconi R. Synovial inflammation drives structural damage in hand osteoarthritis: A narrative literature review. Curr Rheumatol Rev. 2017; 13(1):43-50.
45. Benito MJ, Veale DJ, FitzGerald O, van den Berg WB, Bresnihan B. Synovial tissue inflammation in early and late osteoarthritis. Ann Rheum Dis. 2005;64(9):1263-7.
46. Fox RI. Mechanism of action of hydroxychloroquine as an antirheumatic drug. Semin Arthritis Rheum. 1993;23(2 Suppl 1):82-91.
47. Goldman FD, Gilman AL, Hollenback C, Kato RM, Premack BA, Rawlings DJ. Hydroxychloroquine inhibits calcium signals in T cells: a new mechanism to explain its immunomodulatory properties. Blood. 2000;95(11):3460-6.
48. Gilman AL, Beams F, Tefft M, Mazumder A. The effect of hydroxychloroquine on alloreactivity and its potential use for graft-versus-host disease. Bone Marrow Transplant. 1996;17(6):1069-75.
49. Sperber K, Quraishi H, Kalb TH, Panja A, Stecher V, Mayer L. Selective regulation of cytokine secretion by hydroxychloroquine: inhibition of interleukin 1 alpha (IL-1-alpha) and IL-6 in human monocytes and T cells. J Rheumatol. 1993;20(5):803-8.
50. Vuolteenaho K, Kujala P, Moilanen T, Moilanen E. Aurothiomalate and hydroxychloroquine inhibit nitric oxide production in chondrocytes and in human osteoarthritic cartilage. Scand J Rheumatol. 2005;34(6):475-9.

564 51. Orlowsky EW, Kraus VB**.** The role of innate immunity in osteoarthritis: when our first line of
565 defense goes on the offensive. J Rheumatol. 2015;42(3):363-71.
566 52. Radstake TR, Roelofs MF, Jenniskens YM, Oppers-Walgreen B, van Riel PL, Barrera P, et al.
567 Expression of toll-like receptors 2 and 4 in rheumatoid synovial tissue and regulation by
568 proinflammatory cytokines interleukin-12 and interleukin-18 via interferon-gamma. Arthritis
569 Rheum. 2004;50(12):3856-65.
570 53. Kim HA, Cho ML, Choi HY, Yoon CS, Jhun JY, Oh HJ, et al. The catabolic pathway mediated by
571 Toll-like receptors in human osteoarthritic chondrocytes. Arthritis Rheum. 2006;54(7):2152-
572 63.
573 54. Sillat T, Barreto G, Clarijs P, Soininen A, Ainola M, Pajarinen J, et al. Toll-like receptors in
574 human chondrocytes and osteoarthritic cartilage. Acta Orthop. 2013;84(6):585-92.
575 55. Su SL, Yang HY, Lee CH, Huang GS, Salter DM, Lee HS**.** The (-1486T/C) promoter
576 polymorphism of the TLR-9 gene is associated with end-stage knee osteoarthritis in a
577 Chinese population. J Orthop Res. 2012;30(1):9-14.
578 56. https://www.medicinescomplete.com/mc/bnf/current/PHP6586-hydroxychloroquine-
579 sulfate.htm. Accessed 9th June 2017.
580 57. Haugen IK, Slatkowsky Christensen B, Boyesen P, Sesseng S, van der Heijde D, Kvien TK**.**
581 Increasing synovitis and bone marrow lesions are associated with incident joint tenderness
582 in hand osteoarthritis. Ann Rheum Dis. 2016;75(4):702-8.
583 58. Liu R, Damman W, Reijnierse M, Bloem JL, Rosendaal FR, Kloppenburg M**.** Bone marrow
584 lesions on magnetic resonance imaging in hand osteoarthritis are associated with pain and
585 interact with synovitis. Osteoarthritis Cartilage. 2017;25(7):1093-1099.

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587 **Figure Legends**

588 Figure 1: Unadjusted Hand Pain NRS (past two weeks) with 95% CIs; A) HERO study
589 participants with observed data (primary outcome). B) Structural damage sub-groups (based

590 on Kallman total score); C) Synovitis sub-groups (ultrasound sub-study). HCQ =
591 hydroxychloroquine.
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Table 1: Baseline Characteristics

	All randomised patients (n=248)		All patients included in the primary analysis (n=232)	
	HCQ (n=124)	**Placebo (n=124)**	**HCQ (n=113)**	**Placebo (n=119)**
Age				
N	124	124	113	119
Mean (SD)	62.8 (9.1)	62.5 (9.2)	63.1 (9.3)	62.6 (9.1)
Median (min, max)	64 (41 ,88)	62 (40,83)	64 (41, 88)	62 (40, 83)
Gender				
Male	27 (22%)	18 (15%)	26 (23%)	17 (14%)
Female	97 (78%)	106 (85%)	87 (77%)	102 (86%)
BMI				
N	124	124	113	119
Mean (SD)	28.4 (5.4)	29.3 (6.2)	28.5 (5.4)	29.4 (6.3)
Median (min, max)	28 (15, 45)	28 (19, 45)	28 (15, 45)	28 (19, 45)
Ethnicity				
Caucasian	119 (96%)	120 (97%)	109 (96%)	116 (97%)
South Asian	1 (1%)	1 (1%)	1 (1%)	1 (1%)
East Asian	2 (2%)	1 (1%)	2 (2%)	1 (1%)
Afro-Caribbean	1 (1%)	0 (0%)	1 (1%)	0 (0%)
Other	1 (1%)	2 (2%)	0 (0%)	1 (1%)
Hand pain duration in years				
N	124	124	113	119
Mean (SD)	7.4 (6.4)	7.9 (6.7)	7.7 (6.5)	7.8 (6.8)
Median (min, max)	5 (0.4, 30)	5.5 (1, 30)	6 (0.4, 30)	5.5 (1, 30)
Hand Pain NRS (past 48 hours) [0 none - 10 worst]				
N	124	121	113	117
Mean (SD)	6.9 (1.7)	6.8 (1.8)	6.9 (1.62)	6.8 (1.77)
Median (min, max)	7 (2, 10)	7 (2, 10)	7 (3, 10)	7 (2, 10)
Grip Strength in lbs (average both hands)				
N	124	123	113	119
Mean (SD)	34.4 (19.1)	29.9 (19.3)	34.6 (19.6)	29.4 (18.9)
Median (min, max)	31.3 (0, 114.2)	27.5 (1.0, 95.0)	31.5 (0, 114.2)	26.8 (1.0, 95.0)
AUSCAN Pain [0-20]				
N	124	121	113	117
Mean (SD)	12.3 (2.61)	12.7 (3.00)	12.4 (2.6)	12.7 (3.0)
Median (min, max)	12.5 (4, 18)	13 (4, 20)	13 (4, 18)	13 (4, 20)
AUSCAN Function [0-36]				
N	123	122	112	118
Mean (SD)	20.9 (6.5)	21.7 (6.1)	21.1 (6.4)	21.8 (6.1)
Median (min, max)	22 (1, 34)	21.5 (4, 35)	22 (1, 34)	22 (4, 35)
OAQoL [0-38]				
N	123	121	112	117
Mean (SD)	9.5 (9.5)	10.8 (9.5)	9.8 (9.6)	10.5 (9.5)
Median (min, max)	7 (0, 33)	8 (0, 38)	7 (0, 33)	7 (0, 38)
Total number of painful joints [0-30]				
N	124	124	113	119
Mean (SD)	8.3 (5.9)	8.8 (7.1)	8.5 (5.9)	8.6 (7.0)
Median (min, max)	7 (0, 30)	7 (0, 30)	7 (0, 30)	6 (0, 30)

	All randomised patients (n=248)		All patients included in the primary analysis (n=232)	
	HCQ (n=124)	**Placebo (n=124)**	**HCQ (n=113)**	**Placebo (n=119)**
umber of swollen joints [0-30]				
N	124	124	113	119
Mean (SD)	3.8 (4.2)	3.4 (4.4)	4.0 (4.3)	3.4 (4.4)
Median (min, max)	3 (0, 20)	1 (0, 22)	3 (0, 20)	1 (0, 22)
umber of tender joints [0-30]				
N	124	124	113	119
Mean (SD)	10.4 (6.3)	10.9 (7.3)	10.4 (6.3)	10.8 (7.3)
Median (min, max)	10 (0, 27)	9 (0, 30)	10 (0, 27)	9 (0, 30)
Pain in other joints present	114 (92%)	107 (86%)	103 (91%)	102 (86%)
Number of other painful joints [0-14]				
N	124	123	113	119
Mean (SD)	5.8 (2.8)	5.9 (3.1)	5.9 (2.7)	5.8 (3.0)
Median (min, max)	6 (0, 12)	5 (0, 14)	6 (0, 12)	5 (1, 14)
Kallman total radiograph score				
N	94	94	89	93
Mean (SD)	42.7 (25.9)	47.2 (27.4)	43.9 (25.8)	47.3 (27.5)
Median (min, max)	40 (0, 100)	39 (2, 113)	41 (0, 100)	40 (2, 113)
Medication for hand OA				
Oral NSAIDs	50 (40%)	53 (43%)	49 (43%)	50 (42%)
Topical NSAIDs	22 (18%)	25 (20%)	22 (19%)	23 (19%)
Paracetamol	77 (62%)	75 (60%)	69 (61%)	70 (60%)
Opioids	14 (11%)	16 (13%)	12 (11%)	14 (12%)
Co-codamol	23 (19%)	26 (21%)	22 (19%)	26 (22%)
Other	15 (12%)	20 (16%)	14 (12%)	19 (16%)
Any concomitant analgesic use	111 (90%)	112 (90%)	101 (89%)	107 (90%)
Currently using glucosamine and/or chondroitin	20 (16%)	17 (14%)	19 (17%)	15 (13%)

AUSCAN = Australian/Canadian Hand Osteoarthritis Index; BMI = body mass index; HCQ = hydroxychloroquine; NRS = numerical rating scale; NSAIDs = non-selective anti-inflammatory drugs; OAQoL = Osteoarthritis Quality of Life

Table 2: Estimated Treatment Differences in Mean Hand Pain NRS (last 2 weeks)

Analysis & Follow-up	N	HCQ Mean (95% CI)	N	Placebo Mean (95% CI)	Difference Mean (95% CI)	p-value
Primary Analysis †						
3 months	113	5.54 (5.01, 6.07)	119	5.78 (5.26, 6.29)	0.24 (-0.31, 0.78)	.40
6 months *	113	5.66 (5.13, 6.19)	119	5.49 (4.96, 6.02)	-0.16 (-0.73, 0.40)	.57
12 months	113	5.39 (4.83, 5.92)	119	5.51 (4.98, 6.04)	0.13 (-0.45, 0.72)	.66
Adherence adjusted analysis (CACE) ‡						
6 months	107	5.53 (5.12, 5.94)	103	5.74 (5.29, 6.19)	0.21 (-0.44, 0.86)	.52
Analysis including all randomized participants using multiple imputation §						
3 months	124	5.53 (4.98, 6.08)	124	5.76 (5.22, 6.30)	0.23 (-0.31, 0.78)	.40
6 months	124	5.65 (5.11, 6.18)	124	5.45 (4.89, 6.00)	-0.20 (-0.80, 0.41)	.52
12 months	124	5.38 (4.79, 5.97)	124	5.55 (5.02, 6.08)	0.17 (-0.43, 0.77)	.58
Analysis adjusted for receipt of rescue medication ‖						
3 months	113	5.63 (5.09, 6.17)	119	5.87 (5.34, 6.39)	0.23 (-0.31, 0.78)	.40
6 months	113	5.70 (5.16, 6.23)	119	5.52 (4.99, 6.05)	-0.18 (-0.74, 0.38)	.53
12 months	113	5.36 (4.82, 5.91)	119	5.48 (4.95, 6.01)	0.12 (-0.47, 0.70)	.69

* Primary Endpoint

† Linear mixed effects model with fixed effects of treatment, time, treatment by time interaction, baseline hand pain, age, gender, BMI, baseline grip strength and baseline concomitant analgesic use

‡ Instrumental variable regression(35; Appendix 5) of the outcome at 6 months, accounting for adherence with the active treatment, baseline hand pain, age, gender, BMI, baseline grip strength and baseline concomitant analgesic use

§ Linear mixed effects model with fixed effects of treatment, time, treatment by time interaction, baseline hand pain, age, gender, BMI, baseline grip strength and baseline concomitant analgesic use (any missing data was imputed from analysis covariates using multiple imputation by chained equations) (Appendix 5)

‖ Linear mixed effects model with fixed effects of treatment, time, treatment by time interaction, baseline hand pain, age, gender, BMI, baseline grip strength and baseline concomitant analgesic use and receipt of rescue medication (time varying) (REF: White et al, 2001; Appendix 5)

HCQ = hydroxychloroquine; NRS = numerical rating scale measured using an 11-point (0-10) scale;

Table 3: Key Secondary Outcomes - Mean Estimates from Analysis Models

Outcome & Follow-up	N	HCQ Mean (95% CI)	N	Placebo Mean (95% CI)	Difference Mean (95% CI)	p-value
Pain severity in the most painful joint (NRS over last 2 weeks, range 0-10, higher score = worse pain) *						
3 months	112	5.85 (5.31, 6.40)	119	5.49 (4.96, 6.02)	0.19 (-0.37, 0.75)	.51
6 months	112	6.20 (5.66, 6.75)	119	5.85 (5.31, 6.40)	-0.30 (-0.88, 0.28)	.31
12 months	112	5.83 (5.27, 6.40)	119	6.20 (5.66, 6.75)	-0.09 (-0.70, 0.51)	.76
AUSCAN Pain (Range: 0-20, higher score = worse functioning) †						
3 months	113	11.29 (10.48, 12.11)	117	11.22 (10.42, 12.02)	-0.07 (-0.91, 0.77)	.87
6 months	113	11.14 (10.32, 11.96)	117	10.99 (10.17, 11.81)	-0.15 (-1.02, 0.71)	.73
12 months	113	10.92 (10.08, 11.76)	117	10.38 (9.55, 11.20)	-0.55 (1.44, 0.35)	.23
AUSCAN Function (Range: 0-36, higher score = worse functioning) ‡						
3 months	112	19.61 (18.19, 21.03)	118	20.04 (18.64, 21.43)	0.43 (-1.05, 1.90)	.57
6 months	112	19.51 (18.07, 20.94)	118	19.19 (17.76, 20.61)	-0.32 (-1.84, 1.20)	.68
12 months	112	19.72 (18.24, 21.20)	118	18.74 (17.30, 20.18)	-0.98 (-2.55, 0.59)	.22
Grip Strength Left Hand (in lbs) §						
6 months	105	36.95 (33.26, 40.64)	104	37.98 (34.31, 41.65)	1.03 (-2.75, 4.82)	.59
12 months	105	37.08 (33.31, 40.85)	104	38.85 (35.12, 42.58)	1.77 (-2.14, 5.68)	.38
Grip Strength Right Hand (in lbs) §						
6 months	105	37.34 (33.71, 40.97)	103	37.25 (33.63, 40.88)	-0.09 (-3.87, 3.69)	.96
12 months	105	36.79 (33.08, 40.50)	103	38.89 (35.24, 42.54)	2.10 (-1.80, 5.99)	.29
Kallman Total Radiograph Score (Range: 0-220, higher score = greater structural damage) ‖						
12 months	79	48.14 (47.32, 48.96)	78	48.30 (47.50, 49.10)	0.16 (-0.69, 1.00)	.72
Osteoarthritis Quality of Life (OAQol, range: 0-38, higher score = greater impact of OA symptoms) ¶						
6 months	106	8.60 (7.25, 9.95)	102	8.83 (7.50, 10.17)	0.24 (-1.13, 1.60)	.74
12 months	106	8.96 (7.58, 10.35)	102	9.58 (8.23, 10.94)	0.62 (-0.80, 2.05)	.39
SF-12 Physical Component Score (Range: 0-100, higher score = better functioning) **						
6 months	107	39.63 (37.50, 41.77)	104	39.70 (37.57, 41.82)	0.07 (-2.14, 2.28)	.95
12 months	107	38.32 (36.11, 40.53)	104	40.58 (38.44, 42.72)	2.26 (-0.03, 4.55)	.053
SF-12 Mental Component Score (Range: 0-100, higher score = better functioning) ††						
6 months	107	51.52 (49.34, 53.69)	104	52.24 (50.09, 54.38)	0.72 (-1.57, 3.01)	.54
12 months	107	53.15 (50.89, 55.40)	104	52.00 (49.83, 54.17)	-1.15 (-3.53, 1.24)	.35

* Linear mixed effects model with fixed effects of treatment, time, treatment by time interaction, baseline pain severity, age, gender, BMI, baseline grip strength and baseline concomitant analgesic use

† Linear mixed effects model with fixed effects of treatment, time, treatment by time interaction, baseline AUSCAN pain, age, gender, BMI, baseline grip strength and baseline concomitant analgesic use

‡ Linear mixed effects model with fixed effects of treatment, time, treatment by time interaction, baseline AUSCAN function, age, gender, BMI, baseline grip strength and baseline concomitant analgesic use

§ Linear mixed effects model with fixed effects of treatment, time, treatment by time interaction, baseline grip strength, age, gender, BMI and baseline concomitant analgesic use

|| Linear regression model with fixed effects of treatment, baseline Kallman score, age, gender, BMI, baseline grip strength and baseline concomitant analgesic use

¶ Linear mixed effects model with fixed effects of treatment, time, treatment by time interaction, baseline OAQol, age, gender, BMI, baseline grip strength and baseline concomitant analgesic use

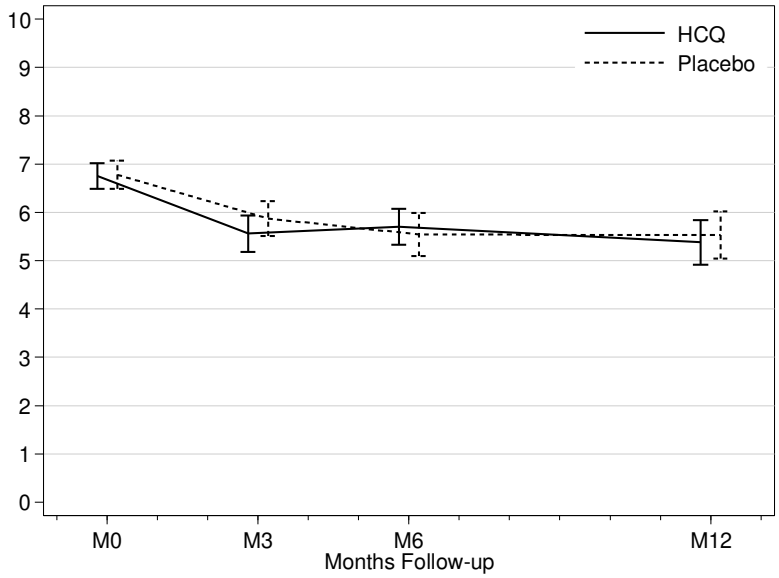
** Linear mixed effects model with fixed effects of treatment, time, treatment by time interaction, baseline SF-12 PCS, age, gender, BMI, baseline grip strength and baseline concomitant analgesic use

†† Linear mixed effects model with fixed effects of treatment, time and treatment by time interaction, adjusted for baseline SF-12 MCS, age, gender, BMI, baseline grip strength and baseline concomitant analgesic use

AUSCAN = Australian/Canadian Hand Osteoarthritis Index; NRS = numerical rating scale; OAQoL = Osteoarthritis Quality of Life; SF-12 = Short Form - 12

Figure 1: Unadjusted Hand Pain NRS (past two weeks) with 95% CIs

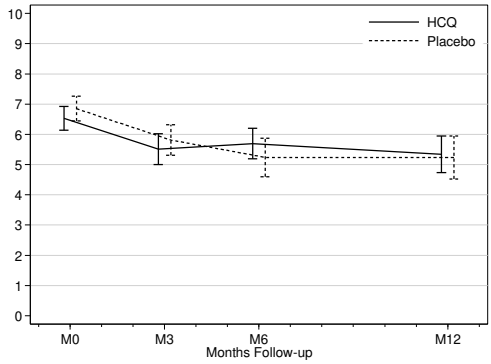
A) HERO study participants with observed data (primary outcome)



HCQ, n	124	109	107	92
Placebo, n	123	119	103	98

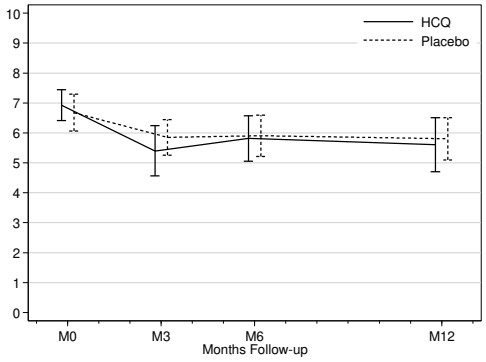
B) Structural damage sub-groups (based on Kallman total score)

Mild to Moderate Structural Damage



HCQ, n	66	61	59	56
Placebo, n	60	59	50	50

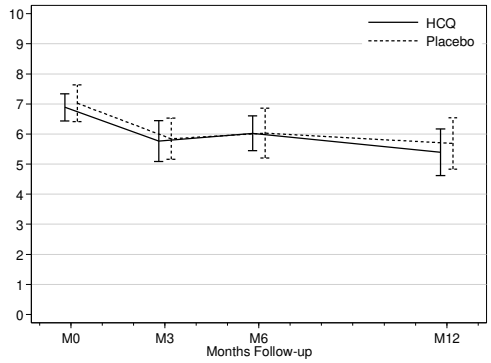
Severe Structural Damage



HCQ, n	28	25	27	23
Placebo, n	34	34	32	31

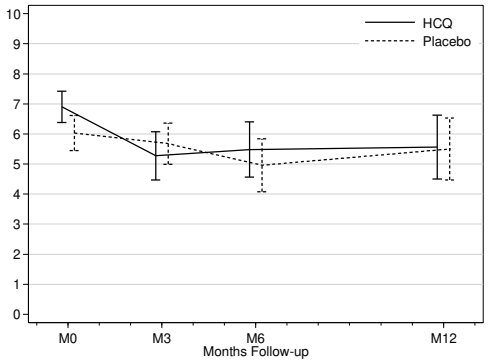
C) Synovitis sub-groups (ultrasound sub-study)

Positive Power Doppler



HCQ, n	45	38	38	33
Placebo, n	39	38	33	32

Negative Power Doppler



HCQ, n	31	29	27	25
Placebo, n	28	28	26	24