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Hydroxychloroquine Effectiveness in Reducing Symptoms of Hand Osteoarthritis

A Randomized Trial

Sarah R. Kingsbury, PhD; Puvan Tharmanathan, PhD; Ada Keding, MSc; Sarah J. Ronaldson, MSc; Andrew Grainger, BMBS; Richard J. Wakefield, MD; Catherine Arundel, MSc; Fraser Birrell, PhD; Michael Doherty, MD; Tonia Vincent, PhD; Fiona E. Watt, PhD; Krysia Dziedzic, PhD; Terence W. O'Neill, MD; Nigel K. Arden, MD; David L. Scott, MD; John Dickson, MBChB; Toby Garrood, PhD; Michael Green, MBChB; Ajit Menon, MD; Tom Sheeran, MD; David Torgerson, PhD; and Philip G. Conaghan, PhD

Background: Synovitis is believed to play a role in producing symptoms in persons with hand osteoarthritis, but data on slow-acting anti-inflammatory treatments are sparse.

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

Design: Randomized, double-blind, placebo-controlled clinical trial with 12-month follow-up. (ISRCTN registry number: ISRCTN91859104)

Setting: 13 primary and secondary care centers in England.

Participants: Of 316 patients screened, 248 participants (82% women; mean age, 62.7 years) with symptomatic (pain ≥4 on a 0- to 10-point visual analogue scale) and radiographic hand osteoarthritis were randomly assigned and 210 (84.7%) completed the 6-month primary end point.

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

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

Results: At 6 months, mean hand pain was 5.49 points in the placebo group and 5.66 points in the hydroxychloroquine group, with a treatment difference of −0.16 point (95% CI, −0.73 to 0.40 point) (P = 0.57). Results were robust to adjustments for adherence, missing data, and use of rescue medication. No significant treatment differences existed at 3, 6, or 12 months for any secondary outcomes. The percentage of participants with at least 1 joint with synovitis was 94% (134 of 143) on grayscale ultrasonography and 59% on power Doppler. Baseline structural damage or synovitis did not affect treatment response. Fifteen serious adverse events were reported (7 in the hydroxychloroquine group [3 defined as possibly related] and 8 in the placebo group).

Limitation: Hydroxychloroquine dosage restrictions may have reduced efficacy.

Conclusion: Hydroxychloroquine was no more effective than placebo for pain relief in patients with moderate to severe hand pain and radiographic osteoarthritis.

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For author affiliations, see end of text.
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Symptomatic hand osteoarthritis affects 4% to 31% of adults older than 70 years and 3% to 15% older than 60 years (1–7). Patients report chronic persistent pain and considerable difficulty with daily activities (8). However, few therapies are effective, and their use is often limited by patients' comorbid conditions or toxicities (9–11). Consequently, primary and secondary care physicians seek alternatives to improve quality of life for persons with this painful, disabling disease. Anecdotal reports suggest hydroxychloroquine (HCQ) as one such therapy. It has been used as an unlicensed treatment in many countries when other options have failed, mainly for patients with "inflammatory" hand osteoarthritis (12, 13). An established drug treatment of inflammatory arthritides, such as rheumatoid arthritis (RA), HCQ is supported by placebo-controlled trials showing its efficacy (as monotherapy and in combination with other RA drugs) and acceptable safety profile (14, 15). Increasing evidence that inflammation is prevalent in osteoarthritis and may have a role in symptoms (16–20) and 3 small pilot studies suggesting reduction in hand pain with HCQ (21–23) provide a rationale for exploring the efficacy of HCQ in treating hand osteoarthritis.

The objective of the HERO (Hydroxychloroquine Effectiveness in Reducing symptoms of hand Osteoarthritis) trial was to test the hypothesis that HCQ is an effective symptomatic treatment when used in persons with at least moderate symptomatic hand osteoarthritis and an inadequate response to current therapies, including nonsteroidal anti-inflammatory drugs (NSAIDs) and opioids.

See also:

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METHODS

Design Overview

HERO was an investigator-led, pragmatic, multicenter, superiority, randomized, 1:1 placebo-controlled trial. The research protocol (Part 1 of the Supplement, available at Annals.org) was approved by the Leeds East Research Ethics Committee and the U.K. Medicines and Healthcare Products Regulatory Agency and registered on ISRCTN (ISRCTN91859104). Participants were recruited from 24 September 2012 until 27 May 2014 and followed up for 12 months after randomization (follow-up completed 25 April 2015). All participants gave written informed consent before screening. One was recruited before protocol registration (24 September 2012 vs. 17 October 2012); however, no changes were made to the protocol between these time points, so this participant is similar to all others. Full trial design details are in the Supplement.

Setting and Participants

The trial involved 13 National Health Service hospitals in England, with recruitment through musculoskeletal clinics in primary and secondary care settings. Eligible patients were aged 18 years or older; reported inadequate response or adverse effects with existing medication (including acetaminophen, oral NSAIDs, and opioids); had moderately severe symptoms (hand pain ≥4 on a 0- to 10-point visual analogue scale) for more than half of days in the past 3 months; fulfilled American College of Rheumatology criteria for osteoarthritis (24); had hand radiographs in the past 5 years with changes consistent with osteoarthritis; had 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 were able and willing to give consent and adhere to the study protocol. Exclusion criteria were inflammatory arthritis; psoriasis; involvement of only the carpometacarpal joint (CMCJ) or predominant CMCJ pain; use of oral, intramuscular, intra-articular, or intravenous steroids, other antisynovial agents, or any new hand osteoarthritis therapies during the past 2 months; intra-articular hyaluronans in the past 6 months; uncontrolled disease states in which flares are commonly treated with corticosteroids; serious uncontrolled medical conditions; unexplained vision impairment; pregnancy or lactation; melanoma or nonskin cancer in the past 3 years; or significant hematologic or biochemical abnormalities (Part 4 of the Supplement). Rheumatoid factor and anticyclic citrullinated peptide were measured in all eligible participants to exclude inflammatory arthritis.

Randomization and Interventions

Patients were randomly assigned to either HCQ (200, 300, or 400 mg, with dosage calculated according to ideal body weight for a maximum of 6.5 mg/kg per day) or placebo. Randomization (1:1) was computer-generated (with PRISYM ClinTrial [PRISYM ID]) in advance by the contract manufacturer using random permuted blocks without stratification. The contract manufacturer prepared the trial drug with overencapsulation 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 blinded to treatment allocation throughout the trial. Adverse events (AEs), vital signs, and blood monitoring were assessed on an ongoing basis during follow-up. All elements of participant care were at the discretion of the site research team, in line with the pragmatic nature of the HERO trial, except that steroids and new or experimental interventions were not permitted during follow-up. Adherence to trial medication was collected using several methods to provide an estimate of compliance, including site-reported nonadherence, a Brief Medication Questionnaire completed by participants (25), and pharmacy records of returned medication. Quality of adherence data was reviewed before unblinding to determine nonadherence criteria for analysis (Part 4 of the Supplement). Staff asked participants about AEs at all visits, and physicians reviewed AEs for severity, duration, and relatedness to the investigational medicinal product. Serious AEs were defined according to prespecified criteria, as detailed in the protocol (Part 1 of the Supplement); assessed for causality and expectedness by a physician; and reported within 24 hours.

Outcomes and Follow-up

Data were collected using standardized case report forms at screening; baseline; and 3, 6, and 12 months. The primary outcome was overall hand pain severity over the past 2 weeks, measured on an 11-point (0-to-10) numerical rating scale (NRS) at 6 months (26). This outcome was also assessed at baseline, 3 months, and 12 months. Secondary outcomes included pain severity in the most painful joint (over the past 2 weeks on the NRS), Australian/Canadian Osteoarthritis Hand Index pain and function scales (27), grip strength (using a dynamometer) (28), structural damage (using bilateral hand radiograph data) (29), Osteoarthritis Quality of Life (30), and Short Form-12 Physical and Mental Component Summary scores (31). Bilateral hand radiographs (baseline and 12 months) were captured according to a standardized protocol (Part 4 of the Supplement) and scored in pairs at the end of the study by a musculoskeletal radiologist who was blinded to participant identity and treatment allocation. Baseline ultrasonography was done for the dominant hand of all participants enrolled at the 7 ultrasonography substudy centers using a standardized protocol (Part 4 of the Supplement) and after a group training day for the ultrasonographers.

A full list of secondary outcomes is in Part 4 of the Supplement and Supplement Table 1 (available at Annals.org). 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, (equal to the reported effect size of NSAIDs as a treatment of hand osteoarthritis [32, 33]) and a reduction in pain of 0.8 point (or 15%) on the

NRS (32, 33), which lies within the minimal clinically important difference for change in pain in a randomized trial (10% to 20%) (34). To detect a standard effect size of 0.4 with 80% power and 5% 2-sided significance, we needed 99 patients per group. Allowing for 20% dropout and equal numbers per center, the total target sample size was 252 patients.

The analyses followed a prespecified statistical analysis plan, endorsed by the data and safety monitoring committee, and were done using Stata, version 13 (StataCorp). The statistician remained blinded to treatment allocation until verification of the primary analysis. The primary analysis was intention-to-treat, analyzing participants in their randomization groups. A linear mixed-effects model was used to analyze 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, and 12 months), treatment group, time-by-treatment interaction, and prespecified covariates (baseline hand pain severity, average grip strength, concomitant analgesic use, age, sex, and body mass index). The model estimate of group differences at 6 months was the primary end point. Because the mixed-effects analysis model incorporated follow-up data from all available time points simultaneously, participants with valid outcome data at 1 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 variables based on self-reported nonadherence, treatment withdrawals, and receipt of corticosteroids; analysis using complier-average causal effect; 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 acetaminophen or steroid injection to the hand, added as a time-varying covariate [36]), all detailed in Part 4 of the **Supplement**. The primary analysis was repeated for participants with osteoarthritis 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 subgroup analyses explored differences in treatment response by level of structural damage (mild or moderate vs. severe, based on Kallman score tertiles) and treatment differences in the presence or absence of synovitis confirmed by ultrasonography (assessed by grayscale, power Doppler, and total synovitis [defined as positive for grayscale or power Doppler]) and osteophytes. Analyses were done by adding an interaction term between treatment allocation and the subgroups to the primary analysis model. In the interest of planning future research, effectiveness was explored across 4 more subgroups hypothesized to affect the treatment mechanism of HCQ, specifically average grip strength (low [<13.6 kg] or high [≥13.6 kg], based on median strength at baseline) and thumb pain (present or absent).

Because of the large number of secondary outcomes, only outcomes of primary clinical interest were analyzed using mixed-effects models, giving treatment effect estimates and *P* values at each follow-up point. The remaining secondary outcomes are reported only descriptively.

Role of the Funding Source

HERO was funded by an Arthritis Research UK clinical studies grant (reference 19545). Arthritis Research UK was 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, 248 participants (74.5%; 124 in each trial group) with hand osteoarthritis from 13 centers in England were recruited and 68 were excluded (**Appendix Figure 1**, available at Annals.org). Baseline characteristics (**Table 1**) were balanced across treatment groups. Participants had had hand pain for a median of 5 years. The participants were predominantly white, 81.9% were women, and the average age was 62.7 years (SD, 9.1). Nearly all (89.9%) were receiving analgesic medication for hand osteoarthritis, and median hand pain over the past 2 weeks was 7 points on the 0- to 10-point NRS. Five participants had elevated levels of rheumatoid factor, and 1 had elevated levels of anti–cyclic citrullinated peptide. Site principal investigators determined all 6 cases to be non–clinically significant and not indicative of inflammatory arthritis.

Most participants (70.6%) were prescribed a 300-mg daily dose of investigational medicinal product (HCQ: 85 participants; placebo: 90 participants) (**Supplement Table 2**, available at Annals.org), with all but 1 continuing to receive the same dose throughout the trial. Balance in characteristics was maintained for patients included in the intention-to-treat analysis. In total, 45 participants (18.1%; HCQ: 24 participants; placebo: 21 participants) did not adhere to the treatment, which is likely to be a conservative estimate, assuming unknown, unreported nonadherence. Those who did not adhere tended to be slightly younger (mean age, 61.2 vs. 63.0 years), with greater average grip strength (16.4 kg vs. 14.2 kg). 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 participants; placebo: 71 participants).

Primary Outcome

Hand pain severity improved for participants with observed data in both groups by around 1 point between baseline and 3 months, and this was maintained up to 12 months (**Figure**, *top*). Outcome data were not available for 20 patients at 3 months, 38 at 6 months, and 58 at 12 months (**Appendix Figure 1**).

We included 232 participants (93.5%; HCQ: 113 participants; placebo: 119 participants) in the primary intention-to-treat analysis. Differences in hand pain

Table 1. Baseline Characteristics*

Characteristic	All Randomly Assigned Patients (n = 248)		Patients Included in the Primary Analysis (n = 232)	
	HCQ (n = 124)	Placebo (n = 124)	HCQ (n = 113)	Placebo (n = 119)
Age, *y*				
Mean (SD)	62.8 (9.1)	62.5 (9.2)	63.1 (9.3)	62.6 (9.1)
Median (range)	64 (41–88)	62 (40–83)	64 (41–88)	62 (40–83)
Sex, *n (%)*				
Male	27 (22)	18 (15)	26 (23)	17 (14)
Female	97 (78)	106 (85)	87 (77)	102 (86)
BMI, *kg/m²*				
Mean (SD)	28.4 (5.4)	29.3 (6.2)	28.5 (5.4)	29.4 (6.3)
Median (range)	28 (15–45)	28 (19–45)	28 (15–45)	28 (19–45)
Ethnicity, *n (%)*				
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)
Duration of hand pain, *y*				
Mean (SD)	7.4 (6.4)	7.9 (6.7)	7.7 (6.5)	7.8 (6.8)
Median (range)	5 (0.4–30)	5.5 (1–30)	6 (0.4–30)	5.5 (1–30)
NRS score for hand pain during the past 48 h†				
Patients, *n*	124	121	113	117
Mean (SD)	6.9 (1.7)	6.8 (1.8)	6.9 (1.6)	6.8 (1.8)
Median (range)	7 (2–10)	7 (2–10)	7 (3–10)	7 (2–10)
Grip strength‡				
Patients, *n*	124	123	113	119
Mean (SD), *kg*	15.6 (8.7)	13.6 (8.8)	15.7 (8.9)	13.3 (8.6)
Median (range), *kg*	14.2 (0–51.8)	12.4 (0.5–43.1)	14.3 (0–51.8)	12.2 (0.5–43.1)
AUSCAN				
Pain score§				
Patients, *n*	124	121	113	117
Mean (SD)	12.3 (2.6)	12.7 (3.0)	12.4 (2.6)	12.7 (3.0)
Median (range)	12.5 (4–18)	13 (4–20)	13 (4–18)	13 (4–20)
Function score‖				
Patients, *n*	123	122	112	118
Mean (SD)	20.9 (6.5)	21.7 (6.1)	21.1 (6.4)	21.8 (6.1)
Median (range)	22 (1–34)	21.5 (4–35)	22 (1–34)	22 (4–35)
OAQoL score¶				
Patients, *n*	123	121	112	117
Mean (SD)	9.5 (9.5)	10.8 (9.5)	9.8 (9.6)	10.5 (9.5)
Median (range)	7 (0–33)	8 (0–38)	7 (0–33)	7 (0–38)
Total painful joints, *n***				
Mean (SD)	8.3 (5.9)	8.8 (7.1)	8.5 (5.9)	8.6 (7.0)
Median (range)	7 (0–30)	7 (0–30)	7 (0–30)	6 (0–30)
Swollen joints, *n***				
Mean (SD)	3.8 (4.2)	3.4 (4.4)	4.0 (4.3)	3.4 (4.4)
Median (range)	3 (0–20)	1 (0–22)	3 (0–20)	1 (0–22)
Tender joints, *n***				
Mean (SD)	10.4 (6.3)	10.9 (7.3)	10.4 (6.3)	10.8 (7.3)
Median (range)	10 (0–27)	9 (0–30)	10 (0–27)	9 (0–30)
Pain in other joints, *n (%)*	114 (92)	107 (86)	103 (91)	102 (86)

Continued on following page

Table 1–Continued

Characteristic	All Randomly Assigned Patients (*n* = 248)		Patients Included in the Primary Analysis (*n* = 232)	
	HCQ (*n* = 124)	Placebo (*n* = 124)	HCQ (*n* = 113)	Placebo (*n* = 119)
Other painful joints, *n*††				
Patients	124	123	113	119
Mean (SD)	5.8 (2.8)	5.9 (3.1)	5.9 (2.7)	5.8 (3.0)
Median (range)	6 (0–12)	5 (0–14)	6 (0–12)	5 (1–14)
Kallman total radiographic score‡‡				
Patients, *n*	94	94	89	93
Mean (SD)	42.7 (25.9)	47.2 (27.4)	43.9 (25.8)	47.3 (27.5)
Median (range)	40 (0–100)	39 (2–113)	41 (0–100)	40 (2–113)
Medication for hand OA, *n (%)*				
NSAIDs				
Oral	50 (40)	53 (43)	49 (43)	50 (42)
Topical	22 (18)	25 (20)	22 (19)	23 (19)
Acetaminophen	77 (62)	75 (60)	69 (61)	70 (60)
Opioids	14 (11)	16 (13)	12 (11)	14 (12)
Codeine–acetaminophen	23 (19)	26 (21)	22 (19)	26 (22)
Other	15 (12)	20 (16)	14 (12)	19 (16)
Any concomitant analgesic use, *n (%)*	111 (90)	112 (90)	101 (89)	107 (90)
Currently receiving glucosamine and/or chondroitin, *n (%)*	20 (16)	17 (14)	19 (17)	15 (13)

AUSCAN = Australian/Canadian Osteoarthritis Hand Index; BMI = body mass index; HCQ = hydroxychloroquine; NRS = numerical rating scale; NSAID = nonsteroidal anti-inflammatory drug; OA = osteoarthritis; OAQoL = Osteoarthritis Quality-of-Life scale.
* Percentages may not sum to 100 due to rounding.
† 0 indicates no pain and 10 indicates worst pain.
‡ Average for both hands.
§ Range, 0–20; higher score indicates worse pain.
‖ Range, 0–36; higher score indicates worse functioning.
¶ Range, 0–38; higher score indicates greater effect of OA symptoms.
** Range, 0–30.
†† Range, 0–14.
‡‡ Range, 0–220.

severity between treatment groups were small at each follow-up and not statistically significant (Table 2 and Figure [*top*]). At the 6-month primary end point, the estimated treatment difference was −0.16 point on the pain NRS (95% CI, −0.73 to 0.40 point) (P = 0.57), that is, participants in the HCQ group reported worse pain by 0.16 point, equal to a standard effect size of 0.07. The CI excludes a clinically meaningful difference in improvement of 0.8 point, on which the trial was powered. Improvements of this magnitude or greater were reported by 58 of 107 patients in the HCQ group and 59 of 103 patients in the placebo group with an NRS pain score reported at 6 months.

Results were robust to secondary analyses of hand pain severity (Table 2). When we used an analysis that accounted for nonadherence, the treatment effect became positive (0.21 point in favor of HCQ), with wide confidence limits (−0.44 to 0.86) that did not exclude the potentially meaningful clinical difference of 0.8 point. When multiple imputation was used to address missing outcome and baseline grip strength data, results were similar to those of the primary analysis of hand pain severity, with similar CI widths (Table 2). Treatment effects of the analysis accounting for rescue medication closely resembled those of the primary analysis of hand pain severity. A repeated analysis for participants with osteoarthritis confirmed on imaging (n = 171 of 182 with imaging data and analysis covariates), as well as estimates treating response time continuously, showed no significant treatment differences (Supplement Table 3, available at Annals.org), with CIs excluding a clinically meaningful difference.

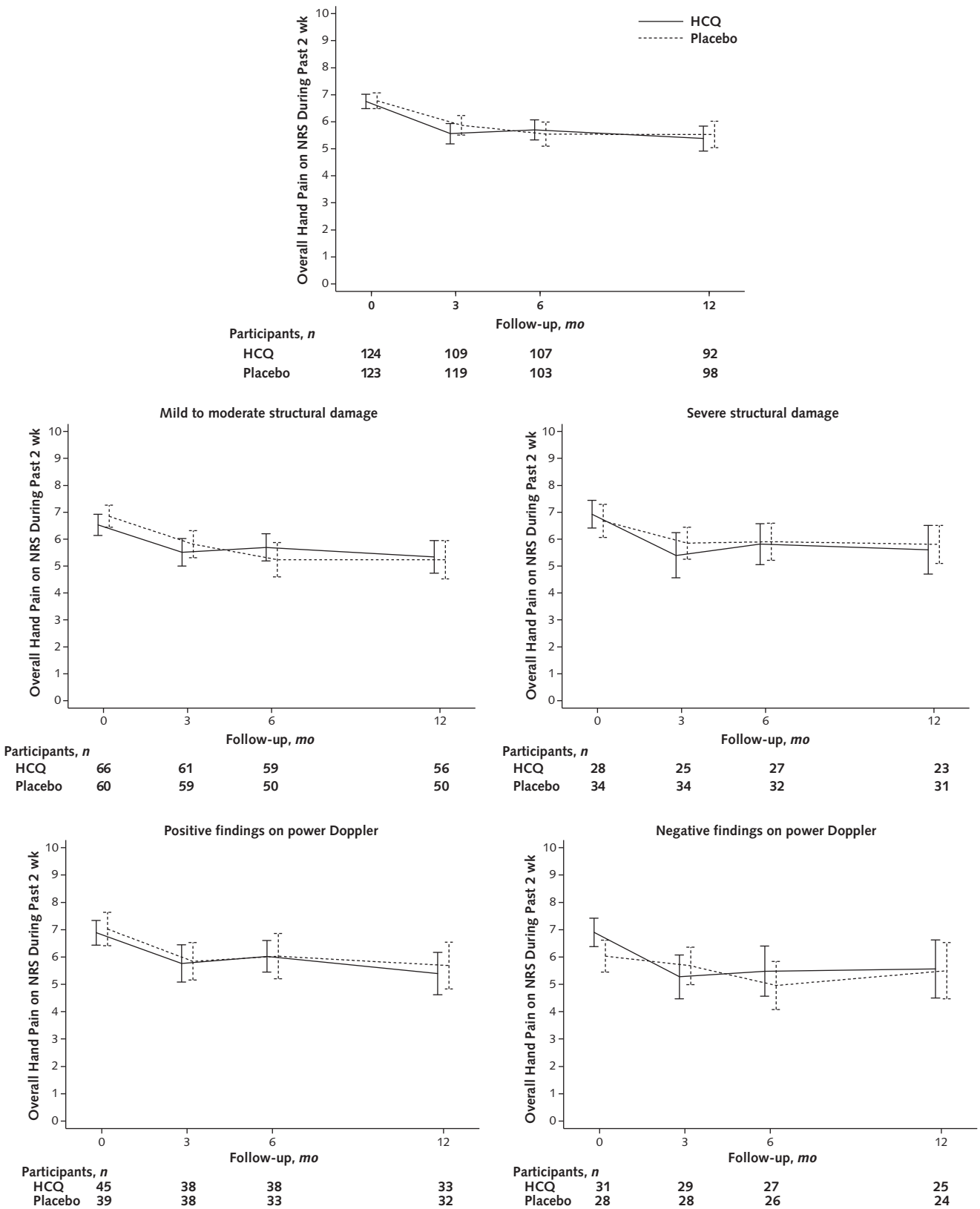
Safety

Fifteen patients reported a total of 15 serious AEs (HCQ: 7 serious AEs; placebo: 8 serious AEs) (Supplement Table 4, available at Annals.org). No deaths were reported. Of the 15 serious AEs, 3 were assessed as being related to HCQ: prolonged QT interval with ventricular arrhythmias, erythema multiforme, and acute generalized erythematous pustulosis.

Secondary Outcomes, Subgroup Analyses, and Ultrasonography Findings

Hand pain and most self-reported symptom outcomes improved in the short term in both groups and then plateaued over follow-up. Mental functioning, grip strength, and structural damage remained unchanged. We found no systematic treatment differences between HCQ and placebo for any secondary outcome (Table 3 and Supplement Table 5, available at Annals.org). A

Figure. Unadjusted hand pain on the NRS in the past 2 weeks, with 95% CIs.



HCQ = hydroxychloroquine; NRS = numerical rating scale. **Top.** Participants with observed data (primary outcome). **Middle.** Structural damage subgroups (based on Kallman total score). **Bottom.** Synovitis subgroups (ultrasonography substudy).

Table 2. Estimated Treatment Differences in Mean Hand Pain on the NRS in the Past 2 Weeks*

Analysis and Follow-up	HCQ		Placebo		Mean Difference (95% CI)	*P* Value
	Patients, *n*	Mean Score (95% CI)	Patients, *n*	Mean Score (95% CI)		
Primary analysis†						
3 mo	113	5.54 (5.01 to 6.07)	119	5.78 (5.26 to 6.29)	0.24 (−0.31 to 0.78)	0.40
6 mo‡	113	5.66 (5.13 to 6.19)	119	5.49 (4.96 to 6.02)	−0.16 (−0.73 to 0.40)	0.57
12 mo	113	5.39 (4.83 to 5.92)	119	5.51 (4.98 to 6.04)	0.13 (−0.45 to 0.72)	0.66
Adherence-adjusted analysis (CACE)§						
6 mo	107	5.53 (5.12 to 5.94)	103	5.74 (5.29 to 6.19)	0.21 (−0.44 to 0.86)	0.52
Analysis including all randomly assigned participants using multiple imputation†‖						
3 mo	124	5.53 (4.98 to 6.08)	124	5.76 (5.22 to 6.30)	0.23 (−0.31 to 0.78)	0.40
6 mo	124	5.65 (5.11 to 6.18)	124	5.45 (4.89 to 6.00)	−0.20 (−0.80 to 0.41)	0.52
12 mo	124	5.38 (4.79 to 5.97)	124	5.55 (5.02 to 6.08)	0.17 (−0.43 to 0.77)	0.58
Analysis adjusted for receipt of rescue medication¶						
3 mo	113	5.63 (5.09 to 6.17)	119	5.87 (5.34 to 6.39)	0.23 (−0.31 to 0.78)	0.40
6 mo	113	5.70 (5.16 to 6.23)	119	5.52 (4.99 to 6.05)	−0.18 (−0.74 to 0.38)	0.53
12 mo	113	5.36 (4.82 to 5.91)	119	5.48 (4.95 to 6.01)	0.12 (−0.47 to 0.70)	0.69

CACE = complier average causal effect; HCQ = hydroxychloroquine; NRS = numerical rating scale.
* Measured using an 11-point scale ranging from 0–10.
† Linear mixed-effects model with fixed effects of treatment, time, treatment-by-time interaction, baseline hand pain, age, sex, body mass index, baseline grip strength, and baseline concomitant analgesic use.
‡ Primary end point.
§ Instrumental variable regression (35) (Part 4 of the **Supplement**, available at Annals.org) of the outcome at 6 mo accounting for adherence to the active treatment, baseline hand pain, age, sex, body mass index, baseline grip strength, and baseline concomitant analgesic use.
‖ Any missing data were imputed from analysis covariates using multiple imputation by chained equations (Part 4 of the **Supplement**).
¶ Linear mixed-effects model with fixed effects of treatment, time, treatment-by-time interaction, baseline hand pain, age, sex, body mass index, baseline grip strength, baseline concomitant analgesic use, and receipt of rescue medication (time varying) (36) (Part 4 of the **Supplement**).

difference of borderline statistical significance (Short Form-12 Physical Component Summary score at 12 months [$P = 0.053$]) could be spurious in light of the number of outcomes and time points assessed.

Radiographic data at baseline, recorded as Kallman scores, were available for 188 participants (75.8%), 94 in each group. We used data tertiles to group observations into mild to moderate damage (score, 0 to 57) and severe damage (score, 58 to 113). Groups did not differ substantially 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**, *middle*). A significant interaction term with treatment allocation ($P = 0.033$) indicated that participants with greater grip strength may benefit more than weaker participants from HCQ treatment (**Appendix Figure 2**, available at Annals.org). A treatment interaction with baseline thumb pain did not show meaningful group differences ($P = 0.136$) (**Appendix Figure 3**, available at Annals.org). Because the latter 2 analyses were exploratory, results may be considered spurious.

A subset of participants had ultrasonography at baseline ($n = 143$ [57.7%]; HCQ: 74 participants; placebo: 67 participants). Most participants had positive findings for synovitis assessed by grayscale (93.7%) and more than half for synovitis assessed by power Doppler (58.7%). All participants had osteophytes in at least 1 joint. We found no significant treatment differences in participants with positive versus negative power Doppler status ($P = 0.85$ for the interaction term with treatment) (**Figure**, *bottom*). Meaningful subgroup analyses were not possible for synovitis assessed by grayscale (only 9 negative cases), total synovitis (power Doppler did not add new cases), or osteophytes.

Discussion

HERO was designed as a pragmatic trial aiming to replicate anecdotal reports of HCQ use in clinical practice and powered to detect a moderate effect equal 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 persons with moderate to severe hand osteoarthritis. The patient population had no demographic differences 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 that HCQ should be considered within the management plan of patients with hand osteoarthritis.

In terms of age, sex, and body mass index, our population reflects that of recent community-based cohorts of hand osteoarthritis in the United Kingdom and Europe (37–40). We deliberately excluded participants with isolated first CMCJ involvement or predominant first CMCJ pain because of the potential differences in mechanism of disease between first CMCJ and distal and proximal interphalangeal joint osteoarthritis. Although slightly more than half of participants had concomitant thumb pain, in line with previous community

studies (37–40) this was not the primary site of hand pain, and treatment effect did not differ between those with and without CMCJ involvement. Consistent with recent imaging studies, synovitis detected by grayscale ultrasonography was common, with nearly all participants having moderate-grade synovitis in at least 1 joint. Power Doppler–detected synovitis, although less common, was present in slightly more than half of participants and was not associated with treatment differences. On the basis of the additional subgroup analyses, weaker grip strength may predispose persons to tenosynovitis or enthesitis, alternative causes of hand pain in this population. This suggests a need to consider grip strength when planning further studies.

A growing body of imaging and experimental evidence suggests that synovitis has a role in the pathogenesis of osteoarthritis and is associated with pain. Ultrasonography-detected synovitis is independently

Table 3. Key Secondary Outcomes: Mean Estimates From Analysis Models

Outcome and Follow-up	HCQ		Placebo		Mean Difference (95% CI)	*P* Value
	Patients, *n*	Mean (95% CI)	Patients, *n*	Mean (95% CI)		
Pain severity in the most painful joint by NRS score over the past 2 wk*						
3 mo	112	5.85 (5.31 to 6.40)	119	5.49 (4.96 to 6.02)	0.19 (–0.37 to 0.75)	0.51
6 mo	112	6.20 (5.66 to 6.75)	119	5.85 (5.31 to 6.40)	–0.30 (–0.88 to 0.28)	0.31
12 mo	112	5.83 (5.27 to 6.40)	119	6.20 (5.66 to 6.75)	–0.09 (–0.70 to 0.51)	0.76
AUSCAN						
Pain score†						
3 mo	113	11.29 (10.48 to 12.11)	117	11.22 (10.42 to 12.02)	–0.07 (–0.91 to 0.77)	0.87
6 mo	113	11.14 (10.32 to 11.96)	117	10.99 (10.17 to 11.81)	–0.15 (–1.02 to 0.71)	0.73
12 mo	113	10.92 (10.08 to 11.76)	117	10.38 (9.55 to 11.20)	–0.55 (1.44 to 0.35)	0.23
Function score‡						
3 mo	112	19.61 (18.19 to 21.03)	118	20.04 (18.64 to 21.43)	0.43 (–1.05 to 1.90)	0.57
6 mo	112	19.51 (18.07 to 20.94)	118	19.19 (17.76 to 20.61)	–0.32 (–1.84 to 1.20)	0.68
12 mo	112	19.72 (18.24 to 21.20)	118	18.74 (17.30 to 20.18)	–0.98 (–2.55 to 0.59)	0.22
Grip strength, *kg*§						
Left hand						
6 mo	105	16.76 (15.09 to 18.43)	104	17.23 (15.56 to 18.89)	0.47 (–1.25 to 2.19)	0.59
12 mo	105	16.82 (15.11 to 18.53)	104	17.62 (15.93 to 19.31)	0.80 (–0.97 to 2.58)	0.38
Right hand						
6 mo	105	16.94 (15.29 to 18.58)	103	16.90 (15.25 to 18.54)	–0.04 (–1.76 to 1.67)	0.96
12 mo	105	16.69 (15.01 to 18.37)	103	17.64 (15.98 to 19.30)	0.95 (–0.82 to 2.72)	0.29
Kallman total radiographic score‖						
12 mo	79	48.14 (47.32 to 48.96)	78	48.30 (47.50 to 49.10)	0.16 (–0.69 to 1.00)	0.72
OAQoL score¶						
6 mo	106	8.60 (7.25 to 9.95)	102	8.83 (7.50 to 10.17)	0.24 (–1.13 to 1.60)	0.74
12 mo	106	8.96 (7.58 to 10.35)	102	9.58 (8.23 to 10.94)	0.62 (–0.80 to 2.05)	0.39
SF-12**						
Physical Component Summary score††						
6 mo	107	39.63 (37.50 to 41.77)	104	39.70 (37.57 to 41.82)	0.07 (–2.14 to 2.28)	0.95
12 mo	107	38.32 (36.11 to 40.53)	104	40.58 (38.44 to 42.72)	2.26 (–0.03 to 4.55)	0.053
Mental Component Summary score‡‡						
6 mo	107	51.52 (49.34 to 53.69)	104	52.24 (50.09 to 54.38)	0.72 (–1.57 to 3.01)	0.54
12 mo	107	53.15 (50.89 to 55.40)	104	52.00 (49.83 to 54.17)	–1.15 (–3.53 to 1.24)	0.35

AUSCAN = Australian/Canadian Osteoarthritis Hand Index; HCQ = hydroxychloroquine; NRS = numerical rating scale; OAQoL = Osteoarthritis Quality-of-Life scale; SF-12 = Short Form-12 Health Survey.
* Linear mixed-effects model with fixed effects of treatment, time, treatment-by-time interaction, baseline pain severity, age, sex, body mass index, baseline grip strength, and baseline concomitant analgesic use. Range, 0–10; higher score indicates worse pain.
† Linear mixed-effects model with fixed effects of treatment, time, treatment-by-time interaction, baseline AUSCAN pain score, age, sex, body mass index, baseline grip strength, and baseline concomitant analgesic use. Range, 0–20; higher score indicates worse pain.
‡ Linear mixed-effects model with fixed effects of treatment, time, treatment-by-time interaction, baseline AUSCAN function score, age, sex, body mass index, baseline grip strength, and baseline concomitant analgesic use. Range, 0–36; higher score indicates worse functioning.
§ Linear mixed-effects model with fixed effects of treatment, time, treatment-by-time interaction, baseline grip strength, age, sex, body mass index, and baseline concomitant analgesic use.
‖ Linear regression model with fixed effects of treatment, baseline Kallman radiographic score, age, sex, body mass index, baseline grip strength, and baseline concomitant analgesic use. Range, 0–220; higher score indicates greater structural damage.
¶ Linear mixed-effects model with fixed effects of treatment, time, treatment-by-time interaction, baseline OAQoL score, age, sex, body mass index, baseline grip strength, and baseline concomitant analgesic use. Range, 0–38; higher score indicates greater effect of osteoarthritis symptoms.
** Range, 0–100; higher score indicates better functioning.
†† Linear mixed-effects model with fixed effects of treatment, time, treatment-by-time interaction, baseline SF-12 Physical Component Summary score, age, sex, body mass index, 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 Mental Component Summary score, age, sex, body mass index, baseline grip strength, and baseline concomitant analgesic use.

associated with radiographic progression of hand osteoarthritis, painful hand joints are associated with the presence of ultrasonography- and magnetic resonance imaging–detected synovitis, and response to intramuscular steroids (believed to work by reducing synovitis) in hand osteoarthritis is associated with higher levels of ultrasonography-detected synovitis at baseline (19, 41–44). However, baseline synovitis in HERO was not linked to treatment effect. Our inclusion criteria may have yielded participants whose level or type of inflammation was not severe: A previous study suggested that early osteoarthritis may be more inflammatory than established osteoarthritis and that molecular pathways driving inflammation may change as the disease progresses (45). By selecting participants with moderate to severe hand osteoarthritis, 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 it is established as a treatment 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 osteoarthritis (48–50) supported HCQ as a potential therapy. More recent data implicate intracellular Toll-like receptors, in particular Toll-like receptor 9, as key mediators of HCQ's anti-inflammatory properties. This is in keeping with growing evidence of the innate immune system's role in rheumatic disease. Although limited evidence suggests that the innate immune system may be important in osteoarthritis pathogenesis (51)—for example, increased Toll-like receptor expression in osteoarthritis tissue (52–55)—this work is still in its infancy. Further understanding of these mechanisms in osteoarthritis may enable stratification according to a defined inflammatory phenotype.

Other potential limitations include restriction of HCQ dosing to the maximum recommended by the British National Formulary, 6.5 mg/kg per day (56), with most patients receiving 300 mg daily. In clinical RA practice, patients may start HCQ therapy at a higher dose (400 mg), with reduction to a lower maintenance dose after 3 to 6 months. However, only 5.6% of the HCQ group were receiving the lowest dose of 200 mg, and we observed no dose–response relation with treatment effect. The co-occurrence of bone marrow lesions detected by magnetic resonance imaging with hand synovitis has been found to worsen pain and, as shown in knee osteoarthritis, may contribute to pain (57, 58). Because bone marrow lesions cannot be detected by ultrasonography or radiography, we could not examine them. The failure of HCQ as an analgesic in this study may reflect its mild anti-inflammatory activity, suboptimal dosing, or that the level or type of inflammation in our population did not match the mechanism of HCQ. However, in light of our results and the previous failure of biological disease-modifying antirheumatic drugs, it is also worth considering that simply treating "macroscopic" or imaging-detected synovitis with such drugs may not be a useful analgesic strategy. Further exploration of the molecular mechanisms of inflammation in osteoarthritis 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 persons selected for moderate to severe hand pain and radiographic osteoarthritis. Our findings in this full-scale pragmatic trial do not support the current practice of off-label use of HCQ in patients with hand osteoarthritis.

From Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds and National Institute for Health Research (NIHR) Leeds Biomedical Research Centre, Leeds, United Kingdom; York Trials Unit, University of York, York, United Kingdom; Institute of Cellular Medicine, Newcastle University, Newcastle upon Tyne, United Kingdom; School of Medicine, University of Nottingham, Nottingham, United Kingdom; Arthritis Research UK Centre for Osteoarthritis Pathogenesis, Kennedy Institute of Rheumatology, University of Oxford, Oxford, and Imperial College Healthcare, London, United Kingdom; Institute for Primary Care and Health Sciences, Arthritis Research UK Primary Care Centre, Keele University, Staffordshire, United Kingdom; Arthritis Research UK Centre for Epidemiology, The University of Manchester, NIHR Manchester Biomedical Research Centre, Central Manchester University Hospitals National Health Service (NHS) Foundation Trust, and Manchester Academic Health Science Centre, Manchester, United Kingdom; Arthritis Research UK Centre for Sport, Exercise and Osteoarthritis, University of Oxford, Oxford, United Kingdom; King's College London, London, United Kingdom; South Tees Hospitals NHS Foundation Trust, Middlesbrough, United Kingdom; Guy's and St Thomas' NHS Foundation Trust, London, United Kingdom; Harrogate and District NHS Foundation Trust, Harrogate, and York Teaching Hospital NHS Foundation Trust, York, United Kingdom; Haywood Hospital, Stoke-On-Trent, United Kingdom; and Cannock Chase Hospital, Cannock, United Kingdom.

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Requests for Single Reprints: Sarah Kingsbury, PhD, Leeds Institute of Rheumatic and Musculoskeletal Medicine and NIHR Leeds Biomedical Research Centre, 2nd Floor Chapel Allerton Hospital, Chapeltown Road, Leeds LS7 4SA, United Kingdom; e-mail, s.r.kingsbury@leeds.ac.uk.

Current author addresses and author contributions are available at Annals.org.

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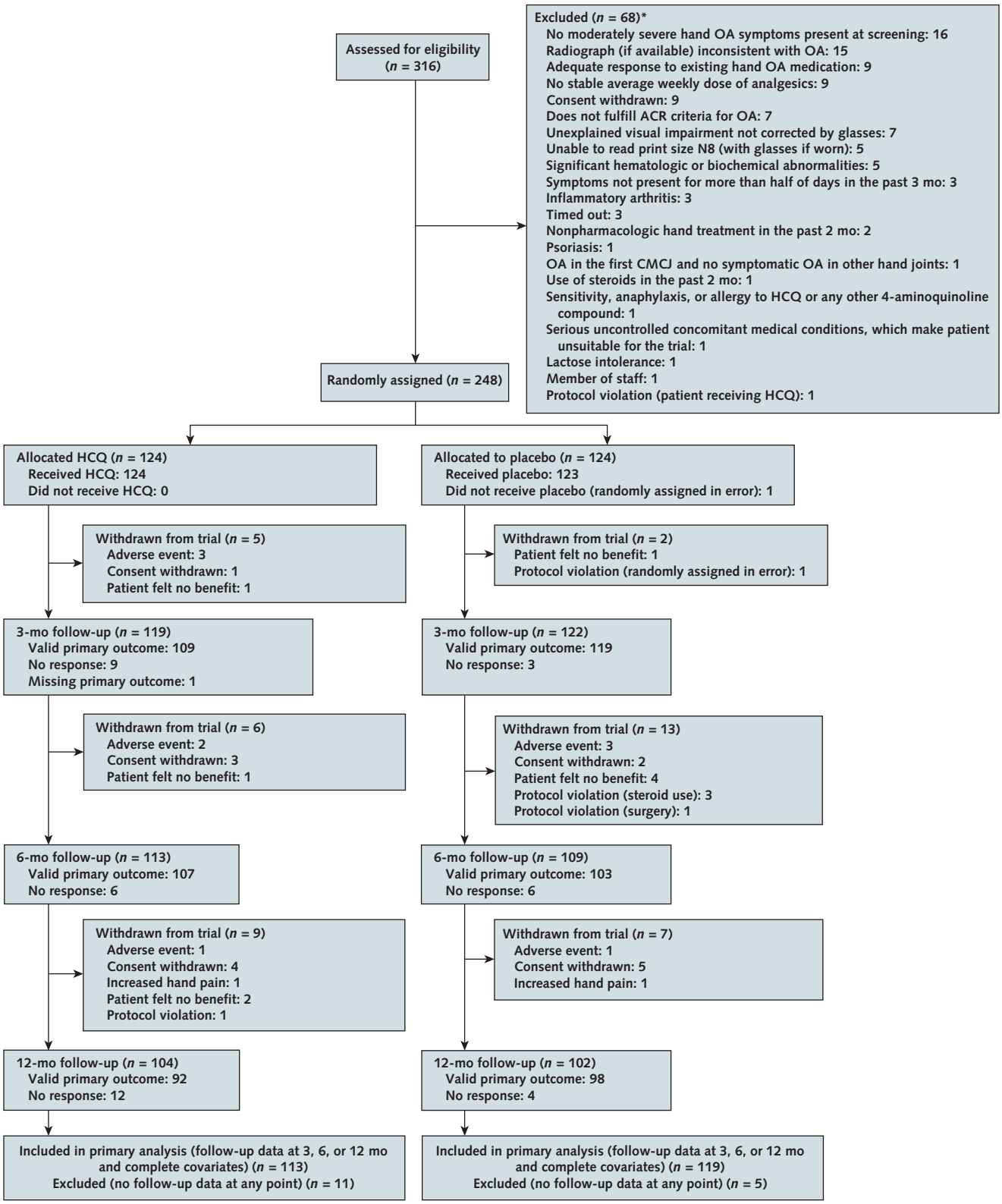
Current Author Addresses: Drs. Kingsbury, Grainger, and Wakefield and Prof. Conaghan: Leeds Institute of Rheumatic and Musculoskeletal Medicine and NIHR Leeds Biomedical Research Centre, 2nd Floor Chapel Allerton Hospital, Chapeltown Road, Leeds LS7 4SA, United Kingdom.
Dr. Tharmanathan, Ms. Keding, Ms. Ronaldson, Ms. Arundel, and Prof. Torgerson: York Trials Unit, Department of Health Sciences, Faculty of Science, University of York, Heslington, York YO10 5DD, United Kingdom.
Dr. Birrell: Institute of Cellular Medicine, Newcastle University, 4th Floor William Leech Building, Medical School, Framlington Place, Newcastle upon Tyne NE2 4HH, United Kingdom.
Prof. Doherty: Academic Rheumatology, Clinical Sciences Building, City Hospital, Nottingham NG5 1PB, United Kingdom.
Prof. Vincent and Dr. Watt: Arthritis Research UK Centre for OA Pathogenesis, Kennedy Institute of Rheumatology, NDORMS, University of Oxford, Roosevelt Drive, Oxford OX3 7FY, United Kingdom.
Prof. Dziedzic: Institute for Primary Care and Health Sciences, Arthritis Research UK Primary Care Centre, Primary Care Sciences, Keele University, Staffordshire ST5 5BG, United Kingdom.
Prof. O'Neill: Arthritis Research UK Centre for Epidemiology, Faculty of Biology, Medicine and Health, The University of Manchester, Oxford Road, Manchester M13 9PL, United Kingdom.
Prof. Arden: Arthritis Research UK Centre for Sport, Exercise and Osteoarthritis, NDORMS, Nuffield Orthopaedic Centre, University of Oxford, Oxford OX3 9DU, United Kingdom.
Prof. Scott: King's College London, Department of Academic Rheumatology, 3rd Floor Weston Education Centre, Cutcombe Road, London SE5 9RJ, United Kingdom.
Dr. Dickson: South Tees Hospitals NHS Foundation Trust, Middlesbrough, Redcar and Cleveland Specialist Musculoskeletal Service, Guisborough Primary Care Hospital, 66 Northgate, Guisborough, Middlesbrough TS14 6HZ, United Kingdom.
Dr. Garrood: Guy's and St Thomas' NHS Foundation Trust, 4th Floor Tower Wing, Guys Hospital, Great Maze Pond, London SE1 9RT, United Kingdom.
Dr. Green: Harrogate and District NHS Foundation Trust, Harrogate District Hospital, Lancaster Park Road, Harrogate HG2 7SX, United Kingdom.
Dr. Menon: Haywood Hospital, High Lane, Burslem, Stoke-On-Trent ST6 7AG, United Kingdom.
Dr. Sheeran: Cannock Chase Hospital, Brunswick Road, Cannock WS11 5XY, United Kingdom.

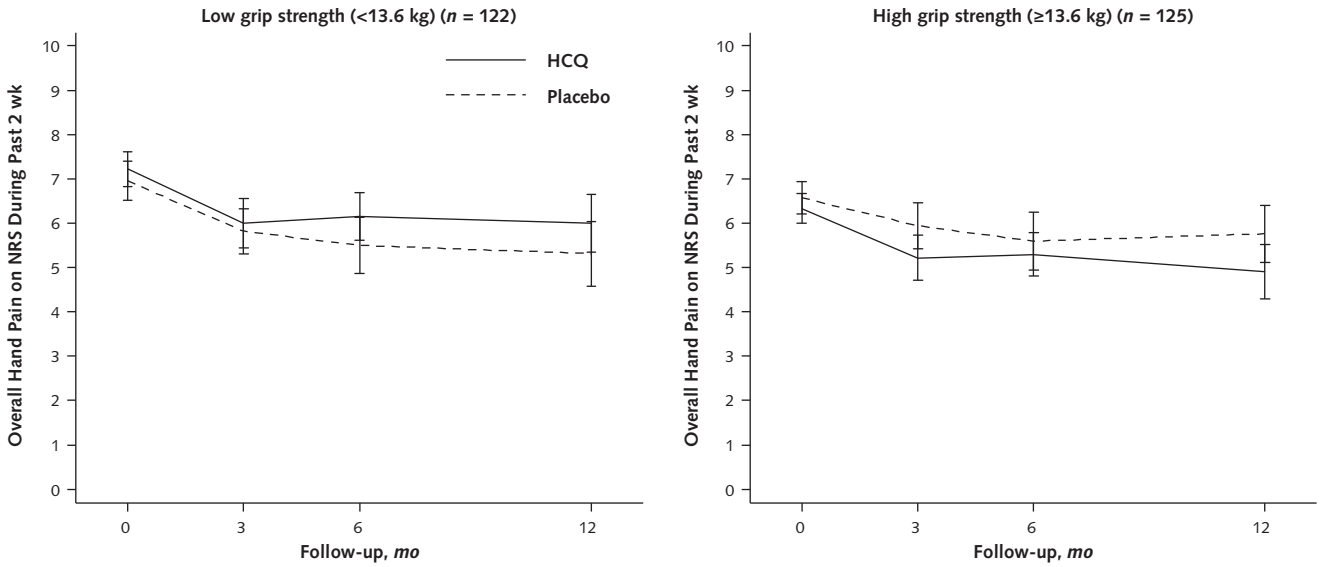
Author Contributions: Conception and design: S.R. Kingsbury, P. Tharmanathan, R.J. Wakefield, M. Doherty, T. Vincent, F.E. Watt, K. Dziedzic, N.K. Arden, D.L. Scott, A. Menon, D. Torgerson, P.G. Conaghan.
Analysis and interpretation of the data: S.R. Kingsbury, P. Tharmanathan, A. Keding, S.J. Ronaldson, A. Grainger, R.J. Wakefield, C. Arundel, F. Birrell, T. Vincent, F.E. Watt, T.W. O'Neill, N.K. Arden, P.G. Conaghan.
Drafting of the article: S.R. Kingsbury, P. Tharmanathan, A. Keding, A. Grainger, C. Arundel, F. Birrell, F.E. Watt, N.K. Arden, T. Sheeran, P.G. Conaghan.
Critical revision of the article for important intellectual content: S.R. Kingsbury, P. Tharmanathan, F. Birrell, M. Doherty, T. Vincent, F.E. Watt, K. Dziedzic, T.W. O'Neill, N.K. Arden, D.L. Scott, D. Torgerson, P.G. Conaghan.
Final approval of the article: S.R. Kingsbury, P. Tharmanathan, A. Keding, S.J. Ronaldson, A. Grainger, R.J. Wakefield, C. Arundel, F. Birrell, M. Doherty, T. Vincent, F.E. Watt, K. Dziedzic, T.W. O'Neill, N.K. Arden, D.L. Scott, J. Dickson, T. Garrood, M. Green, A. Menon, T. Sheeran, D. Torgerson, P.G. Conaghan.
Provision of study materials or patients: F. Birrell, M. Doherty, T. Vincent, F.E. Watt, T.W. O'Neill, D.L. Scott, J. Dickson, A. Menon, P.G. Conaghan.
Statistical expertise: A. Keding, N.K. Arden, P.G. Conaghan.
Obtaining of funding: S.R. Kingsbury, F. Birrell, M. Doherty, T. Vincent, K. Dziedzic, D.L. Scott, M. Green, D. Torgerson, P.G. Conaghan.
Administrative, technical, or logistic support: A. Grainger, F.E. Watt, P.G. Conaghan.
Collection and assembly of data: P. Tharmanathan, R.J. Wakefield, C. Arundel, F. Birrell, T. Vincent, F.E. Watt, T.W. O'Neill, D.L. Scott, M. Green, T. Sheeran, P.G. Conaghan.

Appendix Figure 1. Study flow diagram.



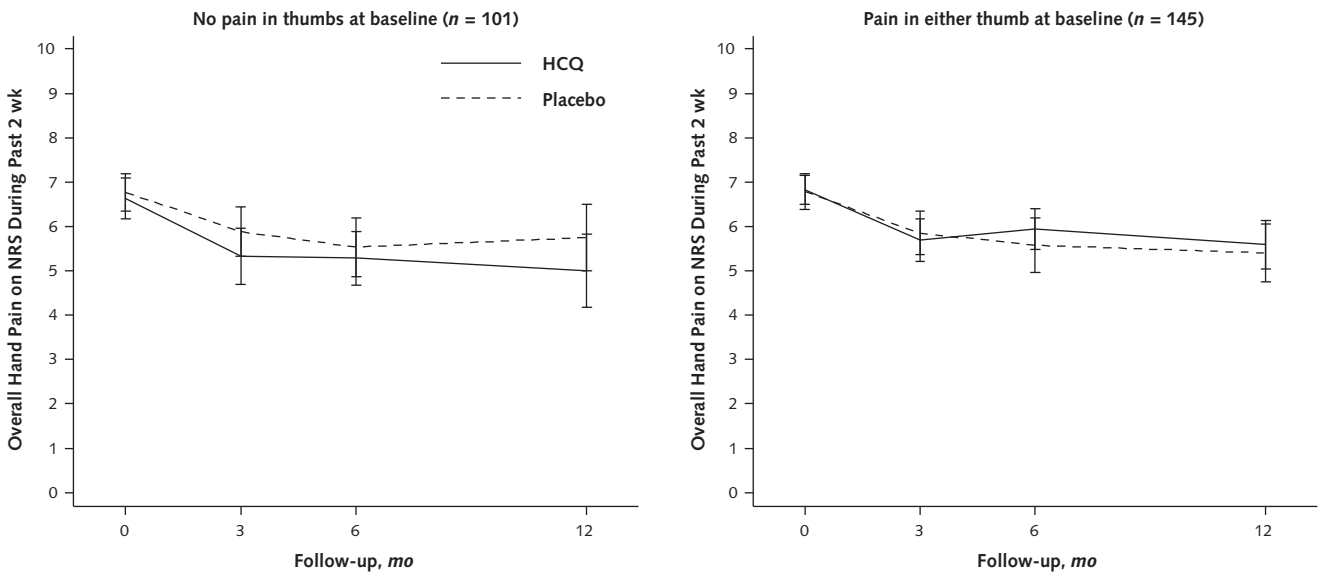
Follow-up categories: valid primary outcome = patient returned questionnaire and primary outcome data were available; missing primary outcome = patient returned questionnaire and primary outcome data were invalid or missing; no response = patient did not return questionnaire. ACR = American College of Rheumatology; CMCJ = carpometacarpal joint; HCQ = hydroxychloroquine; OA = osteoarthritis.
* >1 reason per person possible.

Appendix Figure 2. Hand pain NRS (past 2 weeks), by treatment group and baseline grip strength.



P for interaction = 0.033. HCQ = hydroxychloroquine; NRS = numerical rating scale.

Appendix Figure 3. Hand pain NRS (past 2 weeks), by treatment group and baseline pain in either thumb.



P for interaction = 0.136. HCQ = hydroxychloroquine; NRS = numerical rating scale.