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

3

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43

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46

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49 **Abstract**

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

53  
54 **Objective:** To determine the effectiveness of hydroxychloroquine versus placebo as an  
55 analgesic treatment for hand OA.

56  
57 **Design:** Randomized, double-blind, placebo-controlled clinical trial with 12-month follow-up.

58  
59 **Setting:** 13 primary- and secondary-care centres in England.

60  
61 **Participants:** Of 316 patients screened, 248 participants (82% women, mean age 62.7  
62 years) with symptomatic (VAS pain  $\geq 4/10$ ) and radiographic hand OA were randomized. 210  
63 (84.7%) completed the 6-month primary endpoint.

64  
65 **Intervention:** Hydroxychloroquine (200-400mg) or placebo (1:1) for 12 months in addition to  
66 ongoing usual care.

67  
68 **Measurements:** The primary endpoint was average hand pain during the previous 2 weeks  
69 (numerical rating scale [0-10], NRS) at 6-months. Secondary endpoints included self-  
70 reported pain and function, grip strength, quality-of-life, radiographic structural change and  
71 adverse events. Baseline ultrasonography was performed.

72  
73 **Results:** At 6 months, the mean hand pain (as measured by NRS) was 5.49 and 5.66 in the  
74 placebo and hydroxychloroquine groups, with a treatment difference of -0.16 points (95% CI:  
75 -0.73 to 0.40,  $p=0.57$ ). Results were robust to adjustments for adherence, missing data and  
76 use of rescue medication. There were no significant treatment differences at 3, 6 or 12-

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

81

82 **Limitations:** Hydroxychloroquine dosage restrictions may have reduced efficacy.

83

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

86

87

88

89 Trial Registration: ISRCTN91859104

90 Funding Source: Arthritis Research UK Clinical Studies Grant (19545)

91

92

93 Symptomatic hand osteoarthritis (OA) affects 4-31% of adults over the age of 70, and 3-15%  
94 over the age of 60 (1-7). Individuals report chronic persistent pain and considerable difficulty  
95 with daily activities (8). However there are few effective therapies for this condition and use  
96 of these therapies is often limited by patients' comorbidities or toxicities (9-11). Consequently  
97 primary and secondary care physicians seek alternative options to improve quality of life for  
98 people with this painful, disabling disease. Anecdotal reports suggest hydroxychloroquine  
99 (HCQ) is one such therapy. It has been used as an unlicensed treatment in many countries  
100 when other options have failed, mainly for the subset of patients with "inflammatory" hand  
101 OA (12,13). HCQ is an established drug treatment for inflammatory arthritides such as  
102 rheumatoid arthritis (RA), supported by placebo-controlled trials demonstrating its efficacy,  
103 as a monotherapy and in combination with other RA drugs, and acceptable safety profile  
104 (14,15). With increasing evidence that inflammation is highly prevalent in OA and may have  
105 a role in symptoms (16-20) and three small pilot studies suggesting reduction in hand pain  
106 with HCQ (21-23), there is a rationale for exploring the efficacy of HCQ as a treatment for  
107 hand OA.

108

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

113 **Methods**

114 **Design Overview**

115 The HERO trial was an investigator-led, pragmatic, multi-centre, superiority, randomized, 1:1  
116 placebo-controlled trial. The research protocol (Appendix 1) was approved by Leeds East  
117 Research Ethics Committee (12/YH/0151), the UK Medicines and Health Regulatory  
118 Authority (MHRA) and registered on ISRCTN (ISRCTN91859104) in parallel. Participants  
119 were recruited from September 24<sup>th</sup> 2012 until May 27<sup>th</sup> 2014, with participants followed-up  
120 for 12-months post-randomization (follow-up completed April 25<sup>th</sup> 2015). Written informed  
121 consent was obtained for all participants prior to screening. One participant was recruited  
122 (24.09.2012) prior to protocol registration (17.10.2012), however no changes were made to  
123 the protocol between these time-points and therefore this participant is similar to all other  
124 trial participants. Full trial design details are available (Appendices 1-4).

125

126 **Setting and Participants**

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

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

144

### 145 **Randomization and Interventions**

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

166

### 167 **Outcomes and Follow-up**

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



169 3, 6 and 12-months. The primary outcome was overall hand pain severity over the past 2  
170 weeks, measured on an 11-point (0-10) Numerical Rating Scale (NRS), at 6-months follow-  
171 up (26). This outcome was also assessed at baseline, 3 and 12-months. Secondary  
172 outcomes included: pain severity in the most painful joint (NRS over last 2 weeks), AUSCAN  
173 pain and function scales (27), grip strength (measured using a dynamometer) (28), structural  
174 damage using bilateral hand radiograph data (29), Osteoarthritis Quality of Life (OAQoL)  
175 (30), and Short-form 12 (SF-12) Physical and Mental Component Score (31). Bilateral hand  
176 radiographs (baseline, 12-months) were captured according to a standardized protocol  
177 (Appendix 4) and scored in pairs at the end of the study by a musculoskeletal radiologist  
178 who was blinded to participant identity and treatment allocation. Baseline ultrasound imaging  
179 was performed for the dominant hand of all participants enrolled at the six ultrasound sub-  
180 study centres using a standardised protocol (Appendix 4) and following a group training day  
181 for the ultrasound operators.

182

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

186

### 187 **Statistical Analysis**

188 The HERO trial was powered to detect a standard effect size of 0.4, equivalent to the  
189 reported effect size of NSAIDs as a treatment for hand OA (32,33) and a reduction in pain of  
190 0.8 score points (or 15%) on the NRS (32,33) which lies within the minimal clinically  
191 important difference for change in pain in a randomized trial (10/20%)(34). To detect a  
192 standard effect size of 0.4 with 80% power and 5% two-sided significance, 99 patients were  
193 required per arm. Allowing for 20% dropout and equal numbers per centre, the total target  
194 sample size was 252 patients.

195

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

220

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

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

230

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

234

#### 235 **Role of the funding source**

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

239

#### 240 **Results**

241 Of 316 patients screened, the HERO trial recruited 248 participants (74.5%, 124 in each trial  
242 arm) with hand OA from 13 centres in England, while 68 patients were excluded (Appendix  
243 Figure 1). Baseline characteristics (Table 1) were balanced across treatment arms.

244 Participants were on average 62.7 years old (SD=9.1), 81.9% women, predominantly of  
245 Caucasian ethnicity and had been suffering with hand pain for a median of 5 years. Nearly  
246 all participants (89.9%) were taking analgesic medication for their hand OA, and median  
247 hand pain over the past two weeks was 7 points on the 0 to 10 NRS. Five participants had  
248 raised Rheumatoid Factor (RF) and one had raised anti-cyclic citrullinated peptide (CCP). In  
249 all six cases this was determined to be non-clinically significant by the site PI and not  
250 indicative of inflammatory arthritis.

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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.

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

290

#### 291 Safety

292 A total of 15 serious adverse events (SAEs) were reported by 15 patients (HCQ: 7, placebo:  
293 8; Appendix Table 5). No deaths were reported. Of the 15 SAEs, three were assessed as  
294 being related to HCQ: prolonged QT interval with ventricular arrhythmias, erythema  
295 multiforme and acute generalised erythematous pustulosis.

296

#### 297 Secondary Outcomes, Subgroup Analyses and Ultrasound Findings

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

304

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

315

316 Baseline ultrasound images were taken for a subset of randomized participants ( $n=143$ ,  
317 57.7%; HCQ: 74, placebo: 67). The vast majority were positive for synovitis assessed by  
318 greyscale (93.7%) and over half for synovitis assessed by Power Doppler (58.7%).  
319 Osteophytes were present in at least one joint for all participants. There were no significant  
320 treatment differences between participants with positive or negative Power Doppler status  
321 ( $p=0.85$  for the interaction term with treatment, Figure 1C). Meaningful sub-group analyses  
322 were not possible for greyscale synovitis (only nine negative cases), total synovitis (Power  
323 Doppler did not add new cases) or osteophytes.

324

## 325 **Conclusions**

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

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

335

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

351

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

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

365

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

379

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



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

397

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

402

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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)
<b>Age</b>				
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)
<b>Gender</b>				
Male	27 (22%)	18 (15%)	26 (23%)	17 (14%)
Female	97 (78%)	106 (85%)	87 (77%)	102 (86%)
<b>BMI</b>				
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)
<b>Ethnicity</b>				
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%)
<b>Hand pain duration in years</b>				
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)
<b>Hand Pain NRS (past 48 hours) [0 none - 10 worst]</b>				
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)
<b>Grip Strength in lbs (average both hands)</b>				
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)
<b>AUSCAN Pain [0-20]</b>				
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)
<b>AUSCAN Function [0-36]</b>				
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)
<b>OAQoL [0-38]</b>				
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)
<b>Total number of painful joints [0-30]</b>				
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)	
	<b>HCQ (n=124)</b>	<b>Placebo (n=124)</b>	<b>HCQ (n=113)</b>	<b>Placebo (n=119)</b>
Number 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)
Number 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
<b>Primary Analysis †</b>						
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
<b>Adherence adjusted analysis (CACE) ‡</b>						
6 months	107	5.53 (5.12, 5.94)	103	5.74 (5.29, 6.19)	0.21 (-0.44, 0.86)	.52
<b>Analysis including all randomized participants using multiple imputation §</b>						
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
<b>Analysis adjusted for receipt of rescue medication   </b>						
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
<b>Pain severity in the most painful joint (NRS over last 2 weeks, range 0-10, higher score = worse pain) *</b>						
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
<b>AUSCAN Pain (Range: 0-20, higher score = worse functioning) †</b>						
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
<b>AUSCAN Function (Range: 0-36, higher score = worse functioning) ‡</b>						
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
<b>Grip Strength Left Hand (in lbs) §</b>						
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
<b>Grip Strength Right Hand (in lbs) §</b>						
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
<b>Kallman Total Radiograph Score (Range: 0-220, higher score = greater structural damage)   </b>						
12 months	79	48.14 (47.32, 48.96)	78	48.30 (47.50, 49.10)	0.16 (-0.69, 1.00)	.72
<b>Osteoarthritis Quality of Life (OAQol, range: 0-38, higher score = greater impact of OA symptoms) ¶</b>						
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
<b>SF-12 Physical Component Score (Range: 0-100, higher score = better functioning) **</b>						
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
<b>SF-12 Mental Component Score (Range: 0-100, higher score = better functioning) ††</b>						
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

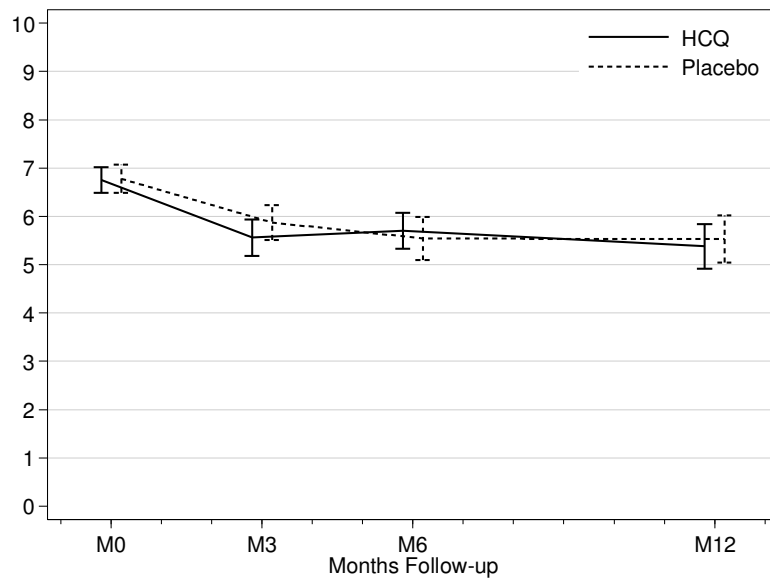
†† Linear mixed effects model with fixed effects of treatment, time and treatment by time interaction, adjusted for baseline SF-12 MCS, age, gender, BMI, baseline grip strength and baseline concomitant analgesic use

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



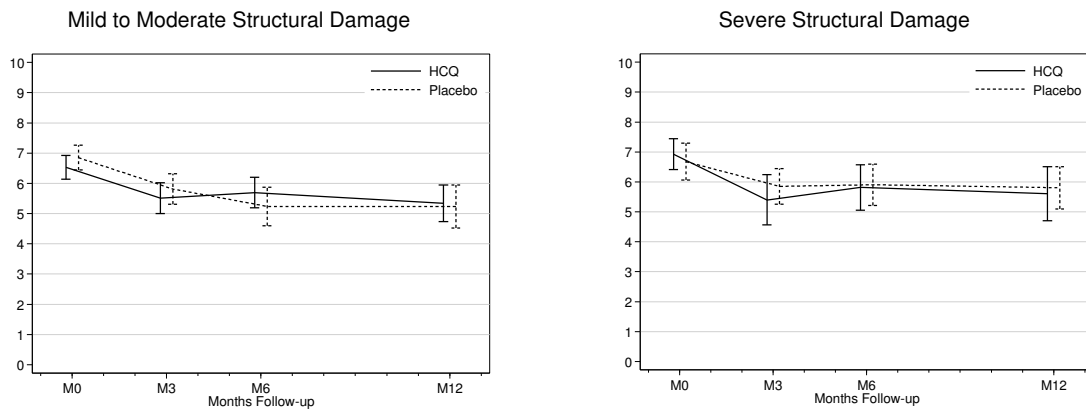
**Figure 1: Unadjusted Hand Pain NRS (past two weeks) with 95% CIs**

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



<b>HCQ, n</b>	124	109	107	92
<b>Placebo, n</b>	123	119	103	98

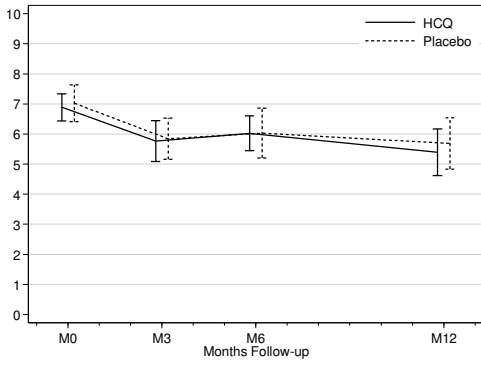
**B) Structural damage sub-groups (based on Kallman total score)**



<b>HCQ, n</b>	66	61	59	56	<b>HCQ, n</b>	28	25	27	23
<b>Placebo, n</b>	60	59	50	50	<b>Placebo, n</b>	34	34	32	31

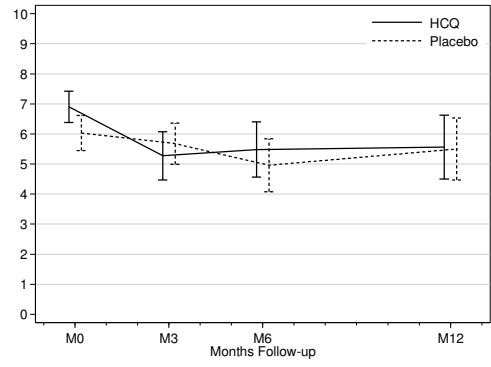
### C) Synovitis sub-groups (ultrasound sub-study)

Positive Power Doppler



<b>HCQ, n</b>	45	38	38	33
<b>Placebo, n</b>	39	38	33	32

Negative Power Doppler



<b>HCQ, n</b>	31	29	27	25
<b>Placebo, n</b>	28	28	26	24