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Colchicine twice daily for hand osteoarthritis: results from the double-blind, randomised, placebo-controlled COLOR trial

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SUMMARY

Background: Colchicine has been suggested for osteoarthritis treatment, but evidence is contradictory. We aimed to investigate colchicine's efficacy and safety compared with placebo in people with hand osteoarthritis.

Methods: In this double-blind, randomised, placebo-controlled trial we recruited adults from an outpatient clinic in Denmark. Eligibility criteria included symptomatic hand osteoarthritis and finger pain of at least 40 mm on a 100-mm visual analogue scale (VAS). The hand with the most severe finger pain at inclusion was the target hand. Participants were randomly assigned to 0·5 mg colchicine or placebo taken orally twice daily for 12 weeks. The primary endpoint was change from baseline to week 12 in target hand finger pain, assessed on a 100-mm VAS with a pre-specified minimal clinically important difference of 15 mm, in the intention-to-treat population. The study was registered prospectively at ClinicalTrials.gov, NCT04601883.

Findings: We screened 186 people for eligibility between January 15, 2021, and March 3, 2022, and randomly assigned 100 participants (mean age 79·9 [SD 7·5] years, 69 [69%] females and 31 [31%] males): 50 (50%) to colchicine and 50 (50%) to placebo.. All participants completed the study. The mean changes from baseline to week 12 in finger pain were -13·9 mm (SE 2·8) in the colchicine group, and -13·5 mm (2·8) in the placebo group with a between-group difference (colchicine versus placebo) of -0·4 mm (95% CI -7·6 to 6·7; p = 0·90). In the colchicine group, there were 76 adverse events in 36 (72%) participants and one serious adverse advent. In the placebo group, there were 42 adverse events in 22 (44%) participants and two serious adverse events.

Interpretation: In people with painful hand osteoarthritis, treatment with 0·5 mg of colchicine twice daily for 12 weeks did not effectively relieve pain and treatment with colchicine was associated with more adverse events.

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Keywords: osteoarthritis, colchicine, hand, randomized, double-blind

RESEARCH IN CONTEXT

Evidence before this study

Hand osteoarthritis is a common joint disease that causes pain, functional disability, decreased quality of life, and societal costs of lost productivity. Inflammation has been implicated in osteoarthritis symptoms, and in people with inflammatory features of hand osteoarthritis and pain flares, glucocorticoids effectively reduce pain and ultrasound synovitis. However, well-known adverse events limit clinical use. Colchicine has anti-inflammatory abilities and could potentially treat the inflammatory aspect of osteoarthritis. Previous clinical trials of colchicine in osteoarthritis have contradictory results. In knee osteoarthritis, nine randomised controlled trials have suggested a beneficial effect of colchicine, whereas two trials found no benefit. We conducted a systematic review of pharmacological treatments for hand osteoarthritis that searched EMBASE, MEDLINE and The Cochrane Central Register of Controlled trials. We searched for randomised clinical trials using synonyms for the aspect osteoarthritis, hands, and management. Each synonym was combined with *OR* and each aspect combined with *AND*. We searched MESH, keywords, and text, but restricted text to title and abstracts. We did the search from inception to September 1, 2022 and found one trial of colchicine for hand osteoarthritis which was underpowered; it reported no difference between colchicine and placebo on hand pain. We hypothesised that colchicine could reduce pain in hand osteoarthritis and designed the present trial to substantiate this.

Added value of this study

In this randomised double-blind placebo-controlled trial, we found no analgesic benefit of treatment with 0·5 mg colchicine twice daily for 12 weeks compared to placebo but considerably more adverse events. Colchicine and placebo were comparable on all pain and function outcome measures, and treatment with colchicine commonly led to gastrointestinal complaints and elevated alanine aminotraferase.

Implications of all the available evidence

Our study provides evidence that colchicine is not a suitable off-label treatment for the pain associated with hand osteoarthritis. Data from this study can be meta-analysed with prior OA colchicine trials to substantiate conclusions. Whether colchicine may have a place in specific subgroups of people remains to be investigated.

INTRODUCTION

Symptomatic hand osteoarthritis (OA) affects 16% of women and 8% of men aged 40-84 years.[1] The lifetime risk of developing symptomatic hand OA is 40% and incidence increases with age.[1,2] People with hand OA experience pain, impaired physical function and reduced health-related quality of life.[3] Hand OA therapies are limited and include non-pharmacological, pharmacological and surgical interventions, but these have only small to moderate effects.[4,5] Non-steroidal anti-inflammatory drugs (NSAIDs), which are widely used, have significant toxicity, especially among older patients in whom hand OA is most prevalent. Therefore, there is a huge unmet need for other effective and safe therapies.

Pain in osteoarthritis is complex but inflammation appears to be one driver, and crystal-induced activation of innate immunity may also play a role.[6] Colchcine down-regulates inflammatory pathwyas by inhibiting neutrophils (adhesion, recruitment, activation, and release), vascular endothelial growth factor and endothelial proliferation.[7] It promotes maturation of dendric cells to act as antigen presenting cells and modulates innate immunerespons by hindering activation of NLRP3 inflammasome (nucleotide-binding oligomerization domain-like receptor pyrin domain-containing-3) and CASPASE-1 (cysteine-dependent aspartate-directed proteases-1). Further, colchicine may be able to modulate innate immuneresponse by interaction with toll like receptor 7.[7,8] Unfortunately, OA trials testing the effectiveness of colchicine show conflicting results and are mainly conducted in people with knee OA.[9-12] Only one trial in hand OA exists and it found no difference between colchicine and placebo.[9] However, this trial was limited by its small sample size, low precision of the pain effect estimate, and did not report the proportion of participants with inflammatory features of hand OA.[9] Thus, there is a need for further studies of colchicine as a treatment of hand OA.

We aimed to investigate the clinical efficacy and safety of oral colchicine 0·5 mg administered twice daily for 12 weeks compared with placebo in people with hand OA. We hypothesized that colchicine was superior to placebo in reducing hand OA pain.

METHODS

The colchicine treatment for people with hand OA (COLOR) study was a single-centre double-blind, randomised, placebo-controlled trial. We recruited eligible adults from the OA outpatient clinic at Bispebjerg and Frederiksberg Hospital, Copenhagen, Denmark. People with a diagnosis of hand OA in follow up at the outpatient clinic were contacted by trial investigators, and if they were interested in trial participation, we prescreened them by telephone interview. Subsequently, an advertisement was placed in a local free newspaper where people could contact trial investigators for information and prescreening. The full trial protocol is available on clinicaltrials.gov, and in the **Appendix p. 53**. Protocol violations were

recorded throughout the study and major protocol violations were defined in the statistical analysis plan, **Appendix p. 12.** Two patient research partners were involved in designing and preparing the study, including review and revision of the protocol and patient information. They focused on study relevance, outcomes and treatment duration and they supported the final study design. Both worked voluntarily. One patient research partner (UD) accepted the invitation to participate in the discussion and interpretation of the results, and reviewing of the manuscript, and qualified as a co-author.

Participants

People were eligible if they had symptomatic hand OA as defined by American College of Rheumatology classification criteria, i.e., hand pain, aching or stiffness on most days the previous four weeks and at least three of the following: hard tissue enlargement of at least two selected joints (selected joints being the 2nd-3rd proximal interphalangeal joint, 2nd-3rd distal interphalangeal joint and the 1st carpometacarpal joint of both hands), hard tissue enlargement of at least two distal interphalangeal joints, fewer than three swollen metacarpophalangeal joints, or deformity of a least one selected joint (see selected joints above).[13] For inclusion, people were required to have finger pain at rest of at least 40 mm on a 100-mm visual analogue scale (VAS). We excluded people who were positive for anti-cyclic citrullinated peptide antibodies, who had elevated levels of serum urate (≥0.35 mmol/L for women under 50 years, ≥0.40 mmol/L for women 50 years or above, and ≥0.48 mmol/L for men) or who had a chronic inflammatory rheumatic disease, psoriasis or any other condition that could cause finger pain; thus, participants with gout, even with normal serum urate, were also excluded. We also excluded people with contraindications to treatment with colchicine i.e. alanine transaminase >45 U/L for women and >70 U/L for men, creatinine clearance ≤60 ml/min, creatine kinase >210 U/L for women and >280 U/L for men, diarrhoea, or treatment with P-glycoprotein inhibitors and/or cytochrome P450 3A4 inhibitors. Full inclusion and exclusion criteria are provided in the trial protocol. Upon inclusion, a target hand was selected corresponding to the hand with the most severe VAS finger pain, as reported by the participants. If this was equal in both hands, we first selected the hand with the highest swollen joint count (physician assessment) and, subsequently, the hand with the highest tender joint count (physician assessment) as the target hand. This hierarchical selection strategy was defined in the protocol (**Appendix p. 71**). Biological sex (male/female) was recorded based on the Danish Central Person Register number (odd = male sex; even = female sex). We did not record ethnicity; most of the OA outpatient clinic's patients are white, and we did not anticipate significant ethnic diversity in our sample. The study was approved by the regional research ethics committee of the Capital Region of Denmark (H-20037713) and conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki. All participants provided written informed consent.

Randomisation and masking

We obtained all baseline measures before randomisation. We randomly assigned participants in a 1:1 ratio to receive colchicine or placebo according to a computer generated randomisation list based on permuted random blocks of variable size (2-12). Randomisation was stratified by body mass index ≥30 kg/m^2, female sex, and age ≥75 years. The Central Pharmacy of The Capital Region, Denmark generated the randomisation list and provided study medication(colchicine 0·5 mg or placebo) in sequentially numbered bottles. We used commercially available colchicine manufactured by Tiofarma, and the Central Pharmacy of the Capital Region manufactured the placebo tablets. The Pharmacy over-encapsulated colchicine and placebo tablets in gelatine to ensure an identical appearance, and packed all study medication. Participants, outcome assessors and data analysts remained masked for treatment allocation until the study database was locked and all analyses described in the statistical analysis plan had been executed and interpreted (**Appendix p. 12 and 43**).

Procedures

We supplied participants with study medication for the entire study period at baseline. Participants self-administered oral intake of 0·5 mg tablets of colchicine or placebo two times daily for 12 weeks. Adherence to trial medication was collected by tablet count at the week 12 study visit and by participant-reported adherence at week 4 and week 12.

Paracetamol and NSAIDs were allowed if stable for 14 days prior to enrolment. Chondroitin sulphate, glucosamine, bisphosphonate, and capsaicin were allowed if stable for three months prior to enrolment. Other pharmacological or surgical treatments for OA were not allowed during the study period, including systemic or intra-articular glucocorticoids, opioids, and immunomodulating therapy. Non-pharmacological interventions were allowed, if stable three months prior to enrolment. Participants were allowed paracetamol up to 4 g daily in case of breakthrough pain. If this was insufficient, NSAIDs up to 1200 mg daily were allowed. Participants recorded NSAIDs and paracetamol use during the study in analgesic diaries.

Physicians (AD and HB) undertook the clinical assessments at baseline and week 12, recording tender and swollen joints (present or absent) at 2^{nd}-5^{th} distal interphalangeal joints, 2^{nd}-5^{th} proximal interphalangeal joints, 1^{st}-5^{th} metacarpophalangeal joints, 1^{st} interphalangeal joint and the 1^{st} carpometacarpal joint. At baseline, physicians also recorded medication use, comorbidities, comorbid joint pain, and symptom duration. Comorbid OA in the knee, hip or other locations was defined by asking the participant whether a doctor at some point had confirmed the OA diagnosis, whereas comorbid joint pain was assessed by systematically asking the participant about current joint pain. Other comorbidities was registered by

combining medical charts with a thorough interview and registered by organ system. Trained nurses undertook the following clinical assessments at baseline: grip strength, blood pressure, height, and weight. Grip strength was assessed as the mean value in Newtons of three repeated measurements in the target hand using a dynamometer (Grippit® AB Detektor, Gothenburg, Sweden). Assessment of grip strength was repeated at week 12. Adverse events were registered throughout the study period and systematically recorded at weeks 4 and 12. Participants were contacted by telephone at week 16 to follow-up any unresolved adverse events.

At baseline, week 4 and week 12, participants completed questionnaires including a VAS of finger pain, a VAS patient global assessment, the Australian-Canadian Hand Osteoarthritis Index (AUSCAN; numeric rating scale format), the European Quality of Life 5 Dimensions (EQ-5D), and a VAS of thumb base pain. When possible, questionnaires were target-hand specific. The week 4 visit was by telephone and questionnaires were answered online. Other visits were in the dedicated outpatient clinic and questionnaires were answered on touch screen.

Ultrasound examinations of the target hand were performed at baseline, to measure signs of inflammation by trained clinicians blinded to the other aspects of the trial. A GE Logiq E10 with a 15 mHz linear transducer and fixed pre-set was used throughout the study. The pre-set had the Doppler adjusted for maximal sensitivity to slow flow. Participants were sitting upright with the target hand resting on a table. The 2^{nd}-5^{th} distal interphalangeal joints, 1^{st}-5^{th} proximal interphalangeal joints, and 2^{nd}-5^{th} metacarpophalangeal joints were examined with hands in the dorsal and volar positions probe in the longitudinal plan. Images were assessed for synovial hypertrophy and for Doppler activity using the OMERACT validated semi-quantitative scoring system (0-3) for each component with higher values indicating more hypertrophy and activity.[14] Presence of inflammation was defined as synovitis Doppler score of ≥1 or synovial hypertrophy score ≥2 in at least one finger joint.

Radiographs of both hands were performed at baseline unless they had been taken in the previous six months. Degenerative status was assessed with the Kellgren-Lawrence system (a grade of 0-4) in the 1^{st} carpometacarpal joint and the 2^{nd}-5^{th} proximal and distal interphalangeal joints in the target hand. We defined erosive OA as presence of erosions in at least one interphalangeal joint (2^{nd}-5^{th} proximal or distal interphalangeal joints) in the target hand.[15]

Fasting blood samples were drawn at screening and week 12 for screening, safety, and exploratory outcomes assessment.

Outcomes

The primary outcome was change from baseline to week 12 in finger joint pain in the target hand using 100-mm VAS with anchors 0 = “no pain” and 100 = “worst possible pain”. Secondary clinical outcomes were change from baseline to week 12 in scores on the AUSCAN pain (scored as 0-50) and function (0-90) subscales,[16] thumb base pain in the target hand (on 100 mm VAS), tender joint count of the target hand (0-15), patient global assessment (on VAS), the EQ-5D (ranging from -0·624 (worst) to 1·000 (best)),[17] grip strength assessment in the target hand in Newtons, and fulfilment of Outcome Measures in Rheumatology-Osteoarthritis Research Society International (OMERACT-OARSI) responder criteria at week 12.[18]
Exploratory outcomes were change from baseline to week 12 in the swollen joint count of the target hand (0-15), C-reactive protein (mg/L), and s-urate (mmol/L). Harms were covered by the number of adverse events, serious adverse events, and withdrawals because of adverse events.
We did a prespecified subgroup analysis of the primary endpoint by degenerative status on radiographs and inflammation on ultrasound. Post-hoc, we did subgroup analysis of the primary endpoint in participants with erosive OA and subgroup analysis by age and symptom duration. We also added post-hoc sex specific assessment of the primary, secondary, and safety outcomes.

Statistical analysis

We considered 15 mm on the VAS as the minimal clinically important difference, adapted from the relative minimal clinically important improvement for the AUSCAN[19] and as previously used in trials of hand OA.[20]
To detect a 15 mm between-group difference in finger pain in the target hand by VAS after 12 weeks (primary outcome) with a standard deviation of 22 mm for change from baseline[20] and an α-level of 0·05 we required 35 participants per group to attain a power of 80% and 46 participants per group to attain a power of 90%. Accounting for an expected 10% loss to follow-up, we sought to include 100 participants in the intention-to-treat population.
We performed the primary analysis using the intention-to-treat population; participants were assessed and analysed as members of their randomised groups, irrespective of adherence to the treatments. We analysed continuous outcomes as change from baseline using repeated measures mixed linear models including participants as random effects, with fixed effect factors for randomisation group, week, and the corresponding interaction (Group×Week), while adjusting for baseline values and the stratification factors (age group, obese body mass index, and sex). Data from all available timepoints were used. Results are reported as least square means with standard errors (SE), and differences between least square means are reported with two-sided 95% confidence intervals (CI). The group difference in the primary outcome was assessed by a two-sided test with an α of 0·05. No explicit adjustments for multiplicity were applied; rather secondary outcomes were analysed and interpreted in a predefined prioritised order (gatekeeping).[21]

Missing data were handled implicitly by the mixed linear model.[22] Dichotomous responder analysis was presented as categorical data and compared using odds ratio. We undertook a prespecified sensitivity analysis for the primary and secondary outcomes as an analysis of covariance adjusted for stratification factors and baseline values with a baseline observation carried forward imputation of missing data. We conducted and interpreted primary, safety and sensitivity analysis blinded to treatment groups, please see **Appendix p. 43**. We presented subgroup analyses with a difference between subgroups and a p-value for interaction. We analysed data with R version 4.0.1, the *nlme* package was used for repeated measures mixed linear models.[23] The statistical analysis plan (**Appendix p. 12**) was finalized on June 17, 2022, before the last participant's last visit.

The study was registered on June 12, 2020, at EudraCT (EudraCT no.: 2020-002803-20) and on October 12, 2020, at clinicaltrials.gov (NCT04601883), and the protocol was finalised on November 24, 2020, before any study-related procedures were commenced. The protocol was not amended or changed during the study. The study was overseen by an independent monitoring committee according to Good Clinical Practice.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the manuscript. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

RESULTS

We screened people for enrolment between January 15, 2021 and March 3, 2022. We prescreened 378 people for eligibility by phone, of these 190 (50%) were not eligible and two (1%) were uable to attend screening in person leaving 186 (49%) people for clinical screening in person. Of the 186 people screened in person 79 (42%) were excluded, predominantly because they did not meet the inclusion criteria of pain or the hand OA classification criteria. 107 (58%) people were eligible for inclusion, but 7 (4%) were not interested in participating after screening, leaving 100 (54%) participants included in the study (**Figure 1**). The participants' mean age was 79·9 [SD 7·5] years, and consisted of 69 [69%] females and 31 [31%] males. We randomly assigned 50 (50%) participants to colchicine and 50 (50%) participants to placebo, all randomised participants were included in the intention-to-treat population and all 100 (100%) participants completed the week 12 study visit and the week 16 follow-up telephone assessment. Six (6%) participants in the colchicine group and four (4%) participants in the placebo group had incomplete electronic questionnaires at week 4. Baseline characteristics were well balanced between the groups (**Table 1** and

Appendix p. 2) with comparable demographics, evidence of inflammation on ultrasound, evidence of erosions on radiographs, comorbidities and outcome measures.

The mean change between baseline and week 12 in VAS finger pain in the target hand are presented in **Table 2.** The mean changes from baseline to week 12 in VAS finger pain were -13·9 mm (SE 2·8) in the colchicine group, and -13·5 mm (2·8) in the placebo group with a between-group difference (colchicine versus placebo) in VAS finger pain in the target hand of -0·4 (95% CI -7·6 to 6·7); p = 0·90 (Table 2). The trajectories of VAS finger pain over the study period are shown in **Figure 2**. No clinically relevant differences were observed in secondary pain and function outcomes, patient global assessment, grip strength and tender joint count (Table 2). EQ-5D scores increased more in the colchicine group than in the placebo group (Table 2). At week 12, 23 (46%) participants in the colchicine group and 22 (44%) participants in the placebo group fulfilled the OMERACT-OARSI responder criteria with no between-group difference. Subgroup analyses of the mean change between baseline and week 12 in VAS finger pain are available in **Appendix p. 6.** Subgroup analyses suggested a higher placebo response among participants ≥75 years and suggested colchicine is effective among participants without erosions on radiographs. Analyses of exploratory outcomes are available in **Appendix p. 7**, with no clinically relevant differences between groups.

The number of non-serious adverse events was higher in the colchicine group than in the placebo group (76 events in 36 (72%) participants in the colchicine group *vs.* 42 events in 22 (44%) participants in the placebo group; **Table 3**). Likewise the number of events "probably related" to treatment was higher in the colchicine group than in the placebo group with 45 and 18 events, respectively. Gastrointestinal complaints were the most common adverse event in both groups followed by elevated alanine aminotransferase (i.e. > 70 U/L for men and >45 U/L for women) in the colchicine group and infections in the placebo group. During our study, three serious adverse events were reported: one in the colchicine group (a migraine attack leading to hospital admission) and two in the placebo group in one participant (first event was cholecystitis, and second event was elevation in alanine aminotransferase, both events occurred simultaneously but was recorded as two events and led to hospital admission for intravenous antibiotic treatment and observation, surgery was done after the participant completed the final study visit). None of these cases were by the investigators categorised as related to the study drugs.

Mean adherence to study medication based on tablet count was 93% (standard deviation 10·6%) in the colchicine group, and 95% (SD 8·6%) in the placebo group. 47 (94%) participants were classified as adherent (intake of at least 80% study medication) in both groups. Self-reported adherence at week 12 with intake of study medication twice daily (i.e., as prescribed) was reported by 45 (90%) participants in the colchicine group and 47 (94%) participants in the placebo group. A summary of self-reported adherence at all timepoints is available in **Appendix p. 4.** All returned capsules were intact with no sign of opening.

Cumulative intake of paracetamol and NSAIDs during the study did not differ between groups, **Appendix p. 8.** Six (17·1%) participants in the colchicine group and 13 (33·3%) participants in the placebo group, who did not take NSAIDs at baseline, received NSAIDs during the study. Two participants (one in each group) had a corticosteroid injection in the upper limb during the study, which was considered protocol violations. Both participants continued the study, and we included them in the primary analysis.

The overall pattern of results for all outcomes was not changed in the sensitivity analysis (**Appendix p. 5**). Similarly, the overall pattern of results was not changed in the sex specific analyses (**Appendix p.9-11**). Raw data for the primary outcome, secondary outcomes, and adverse events separated by sex are available in **Appendix p. 122-131**.

DISCUSSION

In this double-blind, randomised, placebo-controlled trial of colchicine in people with painful hand OA, we found that 12 weeks treatment with 0·5 mg colchicine twice daily was no more effective than placebo in reducing pain. The effect of colchicine was consistently comparable to placebo in secondary outcome measures of pain and function including sensitivity analysis. We found a higher number of adverse events in the colchicine group driven mainly by gastrointestinal complaints.

These results contradict our hypothesis that colchicine would be an effective drug for the pain associated with hand OA. This is despite that 87% of participants in our trial had ultrasound inflammation in the fingers. A more potent anti-inflammatory drug prednisolone has been reported to be effective in reducing pain in people with inflammatory features of hand OA at a dosage of 10 mg per day, but this trial included participants with ultrasound inflammation and added an inclusion criteria of VAS flare-up during 48-hour NSAID washout.[20]

Crystal depositions in the joints, such as monosodium urate and calcium pyrophosphate, mediate inflammation by interleukin-1β maturation in an inflammasome-dependent manner. Stimulating cells with colchicine effectively blocks crystal-induced interleukin-1β maturation, which may be one explanation for the mode of action of colchicine in gout and pseudogout.[24] We hypothesized colchicine to be effective based on the pathogenic role of crystals in OA, but the involvement of crystals in OA, in general, remains to be clarified.

Previous trials of colchicine for knee OA have suggested a beneficial effect on pain, but overall estimates of efficacy from meta-analyses are uncertain with broad confidence intervals.[11] Aside from the difference in OA site, other differences in intervention and study populations could explain the discrepancy with our results. In one study where colchicine was effective, participants were treated with 1·5 mg colchicine daily

for six months and all participants had calcium pyrophosphate crystals verified by polarized light microscopy of the synovial fluid at inclusion, in addition to knee OA.[25] This supports the theory of colchicine as an effective therapy in crystal deposition diseases, but limits generalisability to the overall OA population in which incidence of calcium pyrophosphate crystals in the joint is unknown. Similarly, in two trials where colchicine was effective, 20 out of 36 participants had radiographic chondrocalcinosis and 29 out of 39 participants had calcium pyrophosphate crystals in the synovial fluid, in both trials colchicine was administered as an add-on therapy to NSAIDs, or an add-on to NSAIDs and intra-articular glucocorticoids.[26,27] The add-on strategy was also implemented in other trials showing benefit of colchicine for knee OA, where it was combined with either NSAIDs or paracetamol.[11,12] The lack of efficacy of colchicine is supported by two trials of colchicine 0·5 mg twice daily for three months for people with hand OA and for four months for people with knee OA.[9,28] Our study uses the same intervention and comparator as applied in both studies. The study on knee OA has longer duration but comparable sample size, whereas the hand OA trial is directly comparable with respect to study population, outcomes, and duration. The power in our trial was superior to the previous hand OA trial, which included 32 in each arm and had one participant lost to follow-up in each arm. Our trial also included an extensive description of the study population regarding ultrasound inflammation, comorbidities, comedication, and analgesics that was not addressed in the previous trial. Similarly to our trial, both studies showed higher numbers of adverse events in the colchicine groups driven by gastrointestinal complaint compared to placebo groups.[9,28]

The secondary outcome for the quality of life, EQ-5D, increased more in the colchicine group than in the placebo group. The increase was less than half of the minimal clinically important difference of the EQ-5D for people with knee OA, which suggests limited clinical relevance of this result.[29]

Subgroup analysis suggested that colchicine was effective for people without radiographic erosions, but it could be a type I error and should be confirmed by other trials.

In clinical trials like the COLOR trial, the use of an appropriate comparator (control) group, is necessary to control for factors that might have influenced the measurement of outcomes and accurately assess the true contextual response to a treatment. The placebo response observed in this trial is probably influenced by various factors, including the expectation and beliefs of the participant and the health care provider, and the fact that the OMERACT-OARSI responder criterion is based on patient-reported outcome measures only. Thus, the proportion of improvement in OMERACT-OARSI criteria observed here (for both arms, excluding the likelihood of an effective experimental intervention) constitutes both regression to the mean and a true contextual response due to the clinical attention that is effective *per se*.

The strength of our study is the rigorous methodological design. In addition, the study is adequately powered and all randomised participants completed the final study visit, which makes type II errors less

likely, and the confidence intervals for group difference estimates for both primary and secondary outcomes are well within the predefined minimally clinically relevant difference,[19,20] offering a precise estimate for comparable efficacy of colchicine treatment and placebo.

A limitation of this study is the selected population. It could be argued that evidence of inflammation should have been part of the inclusion criteria, however, as the majority of participants in our trial had ultrasound inflammation, this is only a minor limitation. Another limitation is the dosage, a larger dosage of colchicine may be needed to obtain an effect in hand OA. However, the 0·5 mg twice daily was chosen in our study to reduce the risk of too many treatment failures due to gastrointestinal adverse events. The study medication was over-encapsulated; thus, the tablet inside is potentially identifiable. Returned study medication was intact, and we do not suspect blinding was compromised, but we did not measure the successfulness of blinding. The capsules comply with the European Medicines Agency's requirements for disintegration, and the bioavailability of the tablets was not considered to be affected by over-encapsulation. Finally, we may have overlooked a small treatment benefit as the sample size calculation is based on a medium to large effect size, but this seems clinically reasonable given the abundance of adverse events related to colchicine.

Even though colchicine is not currently recommended for OA, it is used for this indication. This was documented in a randomised controlled trial of people with hand OA showing that 7 of 82 participants (8·5%) reported use of colchicine.[30] Clinically, our results should be used to stop off-label use of colchicine for people with hand OA as our findings do not support this practice. Future research should address whether a sub-population of people with hand OA and crystals could benefit from treatment.

In conclusion, treatment with 0·5 mg of colchicine twice daily for 12 weeks was no more effective than placebo for pain relief in people with painful hand OA, and treatment with colchicine was associated with more adverse events.

CONTRIBUTORS

AD, MH, KE, LKS, FCM, MK, IKH, GMcC, PGC, LT, RDA, FB, EG-N, MB, RC, UD and HB were involved in the design of the study. AD, MH, SMN, RC, and HB made the statistical analysis plan. KE and LJ performed ultrasound examinations; all were scored by KE. AD, LUD, and HB collected the data. HB was the principal investigator. AD and SMN did the statistical analysis. AD, MH, and HB reached consensus on interpretation of results before unblinding. AD wrote the first draft of the manuscript with input from MH and HB. RDA passed away before the final version of the manuscript was finished, he reviewed and approved the first version of the manuscript. All other authors reviewed and approved the final manuscript. AD, MH, HB, and

SMN had full access to all the data in the study. AD and SMN accessed and verified the data. AD, MH, HB, and SMN had final responsibility for the decision to submit for publication.

DECLARATION OF INTEREST

Interests disclosed in the International Committee of Medical Journal Editors (ICMJE) conflict of interest forms are as follows: AD has received grants to this project disclosed in the funding section. FB has received consulting fees from Horizon Therapeutics. FCM has received grants from Innovation Fund Denmark; and payment or honoraria from Varian and Siemens Healthineers. IKH has received grants from Pfizer/Lily (ADVANCE); and payment or honoraria from Novartis and GSK. LT has received payment or honoraria from Eli Lilly, Novartis and Janssen; and is on the advisory board for BMS and Janssen. MH is on the European Advisory Board for Thuasne Group. MGK has received grants from IMI-APPROACH and Dutch Arthritis Society; royalties or licenses from Wolters Kluwer and Springer Verlag; consulting fees for Abbvie, Pfizer, Kiniksa, Flexion, Galapagos, CHDR, Novartis, and UCB; payment or honoraria from Galapagos and Jansen; and is a member of the OARSI board, a member of the EULAR council and President for the Dutch Society for Rheumatology. PGC has received consulting fees from AbbVie, AstraZeneca, Eli Lilly, Galapagos, GlaxoSmithKline, Grunenthal, Janssen, Levicept, Merck, Novartis, Pfizer, Regeneron, Stryker, and UCB; payment or honoraria from AbbVie; and support from AbbVie to congress attendance. LKS has received consulting fees from Pharmac. GMcC has received support for attending meeting from Janssen; and is President for the Irish Society of Rheumatology. EG-N, HB, KE, LJ, LU-MD, RC, SMN, and UD have nothing to disclose.

ETHICAL APPROVAL

This study was approved by the regional research ethics committee of the Capital Region of Denmark (H-20037713).

DATASHARING STATEMENT

Individual participant data that underlie the results reported in this article and analytic code will be available from Henning Bliddal (henning.bliddal@regionh.dk) once all planned analyses have been completed and published. The request will be considered on individual basis. Consent for data sharing was not obtained, but the dataset is anonymised, and risk of reidentification is very low. Study protocol and statistical analysis plan are part of the manuscript. Informed consent form is available upon request.

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FIGURE LEGENDS

Figure 1: Trial profile

*Six participants in the colchicine group and four participants in the placebo group had incomplete electronic questionnaires at week 4.

Figure 2: Visual analogue scale reported pain in the fingers in the target hand for the ITT population.

Data are least squares means with standard errors over the entire study period. ITT, intention-to-treat. VAS, visual analogue scale.