Colchicine twice a day for hand osteoarthritis (COLOR) a double-blind, randomised, placebo-controlled trial

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Citation

Colchicine twice a day for hand osteoarthritis (COLOR): a double-blind, randomised, placebo-controlled 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 single-centre, double-blind, randomised, placebo-controlled trial we recruited adults with symptomatic hand osteoarthritis and finger pain of at least 40 mm on a 100 mm visual analogue scale from an outpatient clinic in Denmark. The hand with the most severe finger pain at inclusion was the target hand. Participants were randomly assigned (1:1) to 0·5 mg colchicine or placebo taken orally twice a day for 12 weeks, stratified by BMI (≥30 kg/m²), sex, and age (≥75 years). Participants, outcome assessors, and data analysts were masked to treatment allocation. The primary endpoint was change from baseline to week 12 in target hand finger pain, assessed on a 100 mm visual analogue scale with a pre-specified minimal clinically important difference of 15 mm, in the intention-to-treat population. Safety was assessed at week 12 in the intention-to-treat population. The study was registered with ClinicalTrials.gov, NCT04601883, and with EudraCT, 2020-002803-20.

Findings Between Jan 15, 2021, and March 3, 2022, 186 people were screened for eligibility, and 100 were randomly assigned to receive colchicine (n=50) or placebo (n=50). Participants had a mean age of 70·9 (SD 7·5) years, 69 (69%) of 100 were women and 31 (31%) were men. All participants completed the study. The mean change 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 vs 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%) of 50 participants and one serious adverse advent (migraine attack leading to hospital admission). In the placebo group, there were 42 adverse events in 22 (44%) of 50 participants and two serious adverse events (cholecystitis and elevated alanine aminotransferase concentrations, in the same patient).

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

Introduction

Symptomatic hand osteoarthritis affects 16% of women and 8% of men aged 40–84 years.[1] The lifetime risk of developing symptomatic hand osteoarthritis is 40%, and incidence increases with age.[1,2] People with hand osteoarthritis experience pain, impaired physical function, and reduced health-related quality of life.[3] Hand osteoarthritis 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 osteoarthritis is most prevalent. Therefore, there is an 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 could also play a role.[6] Colchicine downregulates inflammatory pathways by inhibiting neutrophil functions (adhesion, recruitment, activation, and granule release), production of vascular endothelial growth factor, and endothelial proliferation.[7] It promotes maturation of dendric cells to act as antigen presenting cells and modulates innate immunity by hindering the activation of nucleotide-binding oligomerisation domain-like receptor pyrin domain-containing-3 (NLRP3) inflammasomes and cysteine-dependent aspartate-directed proteases-1 (CASPASE-1). Further, colchicine could modulate innate immune responses by interacting with toll-like receptor 7.[7,8] Unfortunately, trials testing the

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See **Online** for appendix

Research in context

Evidence before this study

Hand osteoarthritis is a common joint disease that causes pain, functional disability, and decreased quality of life; it also incurs societal costs in the form 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 of glucocorticoids. Colchicine has anti-inflammatory properties and could potentially treat the inflammatory aspect of osteoarthritis. Previous clinical trials of colchicine in osteoarthritis have produced contradictory results. In knee osteoarthritis, nine randomised controlled trials have suggested a beneficial effect of colchicine, whereas two trials found no benefit. We searched Embase, MEDLINE, and the Cochrane Central Register of Controlled trials on Dec 26, 2021, for randomised controlled trials of pharmacological treatments for hand osteoarthritis, using the search strategy used to inform the 2018 EULAR recommendations for the treatment for hand osteoarthritis. We searched MESH, keywords, and text, but restricted the text to the title and abstracts. We searched for randomised controlled trials published between database inception and Dec 26, 2021, and found one trial of colchicine for hand osteoarthritis, which was underpowered; it reported no difference between colchicine

and placebo on hand pain. Publications in languages other than Danish, Swedish, Norwegian, German, French, Dutch, Italian, Spanish, or English were excluded from quantitative synthesis. We did an updated search Sept 1, 2022, in the same databases, and we found no new trials for hand osteoarthritis. 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 a day for 12 weeks compared with placebo, with considerably more adverse events in the colchicine group. Colchicine and placebo had similar effects with regard to all pain and function outcome measures, and treatment with colchicine commonly led to gastrointestinal complaints and elevated alanine aminotransferase concentrations.

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 those from previous trials of colchicine for osteoarthritis to substantiate conclusions. Whether colchicine might have a place in specific subgroups of people remains to be investigated.

effectiveness of colchicine in patients with osteoarthritis have shown conflicting results and have mostly been done in people with knee osteoarthritis.[9–12] Only one trial in hand osteoarthritis has been published, which reported 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 absence of information on the proportion of participants with inflammatory features of hand osteoarthritis.[9] Thus, there is a need for further studies of colchicine as a treatment for hand osteoarthritis.

We aimed to investigate the efficacy and safety of oral colchicine 0·5 mg administered twice a day for 12 weeks compared with placebo in people with hand osteoarthritis. We hypothesised that colchicine would be superior to placebo in reducing pain associated with hand osteoarthritis.

Methods

Study design and participants

For this single-centre double-blind, randomised, placebo-controlled trial, we recruited eligible adults from the osteoarthritis outpatient clinic at Bispebjerg and Frederiksberg Hospital, Copenhagen, Denmark. People with a diagnosis of hand osteoarthritis were contacted by trial investigators, and if they were interested in trial participation, were pre-screened by telephone interview. Subsequently, an advertisement was placed in a local free newspaper encouraging eligible people to contact trial

investigators for information and pre-screening. Protocol violations were recorded throughout the study and major protocol violations were defined in the statistical analysis plan (appendix pp 12–41).

People were eligible if they had symptomatic hand osteoarthritis as defined by the 1990 American College of Rheumatology classification criteria.[13] For inclusion, people were required to have finger pain at rest of at least 40 mm on a 100 mm visual analogue scale. Exclusions were positivity for anti-cyclic citrullinated peptide antibodies, elevated concentrations of serum urate (≥0·35 mmol/L for women younger than 50 years, ≥0·40 mmol/L for women aged 50 years or older, and ≥0·48 mmol/L for men), and coexisting chronic inflammatory rheumatic disease, psoriasis, or any other condition that could cause finger pain. As such, participants with gout were excluded, even those with normal serum urate concentrations. We also excluded people with contraindications to treatment with colchicine (eg, 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 or cytochrome P450 3A4 inhibitors). Full inclusion and exclusion criteria are provided in the trial protocol (see protocol; appendix pp 69–71). Upon inclusion, a target hand was selected that corresponded to the hand with the most severe visual analogue scale finger pain, as reported

by the participants. If the visual analogue scale pain 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 (appendix p 71). Biological sex (male and female) was recorded based on the Danish Central Person Register number (odd for male sex and even for female sex). We did not record ethnicity, but most of the patients followed at the osteoarthritis outpatient clinic are White, and we did not anticipate substantial ethnic diversity in our sample.

Two patient research partners (UD and KB) were involved in designing and preparing the study, including review and revision of the protocol and patient information, with a focus on study relevance, outcomes, and treatment duration. Patient partners supported the final study design and worked voluntarily. One patient research partner (UD) participated in the discussion and interpretation of the results and reviewed the manuscript, thereby qualifying as a co-author.

The study was approved by the regional research ethics committee of the Capital Region of Denmark (H-20037713) and was 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. Participants were randomly assigned (1:1) 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 BMI (≥30 kg/m²), sex, and age (≥75 years). Administrative staff booked all visits with no other involvement in the trial, and AD and HB assessed all participants for screening. The Central Pharmacy of The Capital Region (Copenhagen, Denmark) generated the randomisation list and provided study medication (colchicine 0·5 mg or placebo) in sequentially numbered bottles. Participants, outcome assessors, and data analysts were masked to treatment allocation until the study database was locked and all analyses described in the statistical analysis plan had been done (appendix pp 12, 42).

Procedures
We used commercially available colchicine manufactured by Tiofarma (Oud-Beijerland, The Netherlands), and placebo tablets manufactured by the Central Pharmacy of the Capital Region. The pharmacy over-encapsulated the colchicine and placebo tablets in gelatine to ensure an identical appearance and packaged with study medication. Participants were supplied with study medication at baseline and self-administered either colchicine (0·5 mg tablets) or placebo two times a day for 12 weeks. Adherence to trial medication was assessed 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 before enrolment. Chondroitin sulphate, glucosamine, bisphosphonate, and capsaicin were allowed if stable for 3 months before enrolment. Other pharmacological or surgical treatments for osteoarthritis were not allowed during the study period, including systemic or intra-articular glucocorticoids, opioids, and immunomodulatory therapies. Non-pharmacological interventions were allowed if stable for 3 months before enrolment. Participants were allowed paracetamol up to 4 g a day in case of breakthrough pain. If this was insufficient, NSAIDs up to 1200 mg a day 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, including assessment of tender and swollen joints (present or absent) at the 2nd–5th distal interphalangeal joints, 2nd–5th proximal interphalangeal joints, 1st–5th metacarpophalangeal joints, 1st interphalangeal joint, and the 1st carpo-metacarpal joint. At baseline, physicians also recorded medication use, comorbidities, comorbid joint pain, and symptom duration. Comorbid osteoarthritis in the knee, hip, or other locations was determined by asking participants whether a doctor had confirmed the osteoarthritis diagnosis at any time, whereas comorbid joint pain was assessed by systematically asking the participant about current joint pain. Other comorbidities were registered by organ system by combining medical charts with a thorough patient interview. 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 visual analogue scale of finger pain, a visual analogue scale 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 visual analogue scale of base-of-thumb 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 done 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 2nd–5th distal interphalangeal joints, 1st–5th proximal interphalangeal joints, and 2nd–5th metacarpophalangeal joints were examined with hands in the dorsal and volar position and with the probe in the longitudinal plane. Images were assessed for synovial hypertrophy and for Doppler activity using the outcome measures in rheumatology (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 greater or synovial hypertrophy score of 2 or greater in at least one finger joint.

Radiographs of both hands were done at baseline unless they had been taken in the previous 6 months. Degenerative status was assessed with the Kellgren–Lawrence system (graded 0–4) in the 1st carpometacarpal joint and the 2nd–5th proximal and distal interphalangeal joints in the target hand. We defined erosive osteoarthritis as presence of erosions in at least one interphalangeal joint (2nd–5th 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 visual analogue scale 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 subscale (scored as 0–50) and function subscale (0–90),[16] base-of-thumb pain in the target hand (on 100 mm visual analogue scale), tender joint count of the target hand (0–15), patient global assessment (on visual analogue scale), 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 serum 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. We did post-hoc subgroup analyses of the primary endpoint in participants with erosive osteoarthritis and 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 visual analogue scale 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 osteoarthritis.[20] To detect a 15 mm between-group difference in finger pain in the target hand by visual analogue scale after 12 weeks (primary outcome) with an SD 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. We analysed continuous outcomes as change from baseline using repeated measures mixed linear models including participants as random effects,
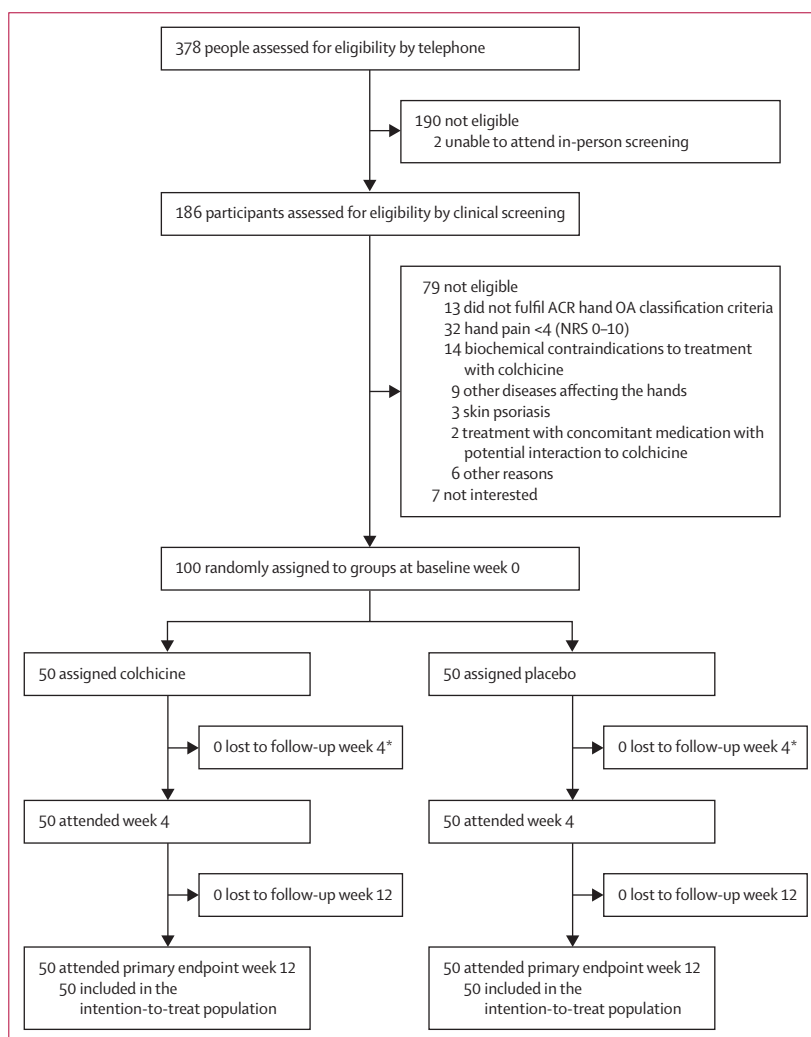

Figure 1: Trial profile
ACR=American College of Rheumatology. OA=osteoarthritis. NRS=numeric rating scale. *Six participants in the colchicine group and four participants in the placebo group had incomplete electronic questionnaires at week 4.

	Colchicine (n=50)	Placebo (n=50)	Total (n=100)
Demographics			
Age (years)	71·2 (7·5)	70·6 (7·6)	70·9 (7·5)
Age (≥75 years)	17 (34%)	15 (30%)	32 (32%)
Female sex	34 (68%)	35 (70%)	69 (69%)
Male sex	16 (32%)	15 (30%)	31 (31%)
BMI (kg/m²)	26·4 (3·8)	26·4 (4·1)	26·4 (3·9)
BMI (≥30 kg/m²)	10 (20%)	11 (22%)	21 (21%)
Symptom duration (years)	12·5 (8·4)	12·9 (9·3)	12·7 (8·8)
Dominant hand as target hand	34 (68%)	29 (58%)	63 (63%)
Ultrasound features of the fingers*			
Inflammation	43 (86%)	44 (88%)	87 (87%)
2nd–5th MCP inflammation	14 (28%)	6 (12%)	20 (20%)
2nd–5th PIP inflammation	34 (68%)	38 (76%)	72 (72%)
2nd–5th DIP inflammation	22 (44%)	30 (60%)	52 (52%)
Color Doppler grade ≥1 in at least one finger joint	21 (42%)	27 (54%)	48 (48%)
Synovial hypertrophy grade ≥2 in at least one finger joint	40 (80%)	42 (84%)	82 (82%)
Doppler sum score (0–36)	0·0 (0·0–1·8)	1·0 (0·0–2·0)	0·0 (0·0–2·0)
Synovial hypertrophy sum score (0–36)	8·3 (3·5)	8·9 (3·9)	8·6 (3·7)
Radiographic features of the fingers†			
Erosions	33 (66%)	36 (72%)	69 (69%)
Kellgren–Lawrence sum grade (0–32)	17·0 (14·2–21·0)	20·5 (14·0–25·0)	19·0 (14·0–24·2)
Number of finger joints with Kellgren–Lawrence ≥2 (0–8)	6·0 (4·0–8·0)	7·0 (4·2–8·0)	6·0 (4·0–8·0)
Comorbidities			
Knee osteoarthritis	20 (40%)	20 (40%)	40 (40%)
Hip osteoarthritis	7 (14%)	7 (14%)	14 (14%)
Other osteoarthritis	21 (42%)	19 (38%)	40 (40%)
Systolic blood pressure (mm Hg)	152·2 (23·2)	148·8 (19·7)	150·5 (21·5)
Diastolic blood pressure (mm Hg)	89·1 (11·1)	88·2 (11·1)	88·6 (11·0)
Concomitant medication‡			
Non-steroid anti-inflammatory drugs	13 (26%)	6 (12%)	19 (19%)
Paracetamol	16 (32%)	14 (28%)	30 (30%)
Statins	19 (38%)	16 (32%)	35 (35%)
Primary outcome measure baseline			
VAS pain fingers target hand (0–100; mm)	47·1 (19·8)	53·5 (18·9)	50·3 (19·5)
Secondary outcome measures baseline			
VAS patient global assessment (0–100; mm)	47·1 (23·1)	50·5 (22·0)	48·8 (22·5)
AUSCAN function (0–90)	44·2 (19·2)	43·3 (20·5)	43·8 (19·8)
AUSCAN pain (0–50)	25·5 (9·8)	26·8 (8·5)	26·2 (9·2)
Grip strength target hand (N)	159·9 (69·3)	148·7 (67·9)	154·3 (68·5)
EQ-5D quality of life (−0·624 to 1·000)	0·784 (0·064)	0·779 (0·069)	0·782 (0·066)
Tender joint count (0–15)	4·1 (3·0)	4·3 (2·5)	4·2 (2·7)
VAS pain thumb base target hand (0–100; mm)	42·0 (29·5)	43·1 (25·4)	42·5 (27·4)

Data are n (%), median (IQR), or mean (SD), unless otherwise stated. AUSCAN=Australian/Canadian hand index score. DIP=distal interphalangeal. EQ-5D=European Quality of Life 5 Dimensions. MCP=metacarpophalangeal. PIP=proximal interphalangeal. VAS=visual analogue scale. *Metacarpophalangeal joints 2 to 5, and proximal and distal interphalangeal joints 2 to 5 in the target hand. †Proximal and distal interphalangeal joints 2 to 5 in the target hand. ‡Used in the last week before baseline.

Table 1: Baseline characteristics of the intention-to-treat population

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, BMI ≥30 kg/m², and sex). Data from all available timepoints were used.

Results were reported as least square means with SEs, and differences between least square means were reported with two-sided 95% CIs. The between-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). Missing data were handled implicitly by the mixed linear model.[21] Dichotomous responder analysis was presented as categorical data and compared using odds ratio (OR). 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. We performed subgroup analyses with comparison between subgroups and a p value for interaction. We analysed data with R, and the nlme package was used for repeated measures mixed linear models. The statistical analysis plan (appendix pp 12–41) was finalised on June 17, 2022, before the last participant's final visit.

This study was registered on June 12, 2020, at EudraCT (EudraCT number 2020-002803-20) and on Oct 12, 2020, with ClinicalTrials.gov, NCT04601883, and the protocol was finalised on Nov 24, 2020, before any study-related procedures 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 report.

Results
Between Jan 15, 2021, and March 3, 2022, 186 people were screened for enrolment. Prior to enrolment screening, 378 people were pre-screened for eligibility by telephone, of whom 190 (50%) were not eligible and two (1%) were unable to attend in-person screening. Of 186 individuals screened in person, 79 (42%) were excluded, predominantly because of insufficient levels of hand pain or not meeting the hand osteoarthritis classification criteria. 107 (58%) people were eligible for inclusion, but seven (4%) were not interested in participating after screening, leaving 100 (54%) participants included in the study (figure 1). The participants' mean age was 70·9 (SD 7·5) years; 69 (69%) of 100 were women and 31 (31%) were men (table 1). We randomly assigned 50 (50%) to colchicine and 50 (50%) participants to placebo. All randomised participants were

included in the intention-to-treat population and all participants completed the week 12 study visit and the week 16 follow-up telephone assessment (figure 1). Six (12%) of 50 participants in the colchicine group and four (8%) of 50 participants in the placebo group had incomplete electronic questionnaires at week 4.

The mean change from baseline to week 12 in visual analogue scale 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 *vs* placebo) of –0·4 (95% CI –7·6 to 6·7; p=0·90; table 2). The trajectories of visual analogue scale 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, or 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%) of 50 participants in the colchicine group and 22 (44%) participants in the placebo group fulfilled the OMERACT-OARSI responder criteria with no difference between groups. Subgroup analyses suggested a higher placebo response among participants aged 75 years and older and that colchicine might be more effective among participants without erosions on radiographs (appendix p 6). No clinically relevant differences were noted in exploratory outcomes (appendix p 7).

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 and 42 events in 22 [44%] participants in the placebo group; table 3). Likewise, the number of adverse events probably related to treatment was higher in the colchicine group (n=45) than in the placebo group (n=18). Gastrointestinal complaints were the most common adverse event in both groups followed by elevated alanine aminotransferase concentrations (ie, >70 U/L for men and >45 U/L for women) in the colchicine group and infections in the placebo group. During the 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 (cholecystitis and elevated alanine aminotransferase concentrations [both events occurred simultaneously but were recorded as two events], leading to hospital admission for intravenous antibiotic treatment and observation [surgery was done after the participant completed the final study visit]). None of the serious adverse events were categorised as related to the study drugs by the investigators.

Mean adherence to study medication based on tablet count was 93% (SD 11%) in the colchicine group, and 95% (9%) in the placebo group. 47 (94%) of 50 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 as prescribed (ie, twice a day) was reported by 45 (90%) of 50 participants in the colchicine group and 47 (94%) of 50 participants in the placebo group

(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%) of 35 participants in the colchicine group and 13 (33%) of 39 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 were 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) or the sex-specific analyses (appendix pp 9–11). Raw data for the

	Colchicine (n=50)	Placebo (n=50)	Difference between groups (95% CI)	p value
Primary outcome				
VAS pain fingers target hand (0–100; mm)	–13·9 (2·8)	–13·5 (2·8)	–0·4 (–7·6 to 6·7)	0·90
Secondary outcomes				
VAS patient global assessment (0–100; mm)	–12·4 (2·8)	–11·2 (2·8)	–1·2 (–8·3 to 5·9)	*
AUSCAN function (0–90)	–10·5 (2·1)	–8·3 (2·1)	–2·2 (–7·6 to 3·2)	*
AUSCAN pain (0–50)	–7·8 (1·2)	–5·3 (1·2)	–2·4 (–5·4 to 0·5)	*
Grip strength target hand (N)	9·4 (4·0)	14·1 (4·0)	–4·7 (–14·8 to 5·4)	*
EQ-5D quality of life (–0·624 to 1·000)	0·032 (0·011)	0·000 (0·011)	0·032 (0·004 to 0·060)	*
Tender joint count target hand (0–15)	–1·0 (0·2)	–0·8 (0·2)	–0·2 (–0·7 to 0·4)	*
VAS pain base-of-thumb target hand (0–100; mm)	–11·9 (2·8)	–10·0 (2·8)	–1·9 (–9·0 to 5·1)	*
OMERACT-OARSI responders†	23 (46%)	22 (44%)	OR 1·1 (0·5 to 2·5)	*

Data are n (%), group values are least squares means (SE), and contrasts are differences in least square means (95% CIs), unless otherwise stated. AUSCAN=Australian/Canadian hand index score. EQ-5D=European Quality of Life 5 Dimensions. OMERACT-OARSI=Outcome Measures in Rheumatology-Osteoarthritis Research Society International. VAS=visual analogue scale. *As no significant effect was found for the primary outcome, p values are not reported for subsequent analysis according to gatekeeping. †OMERACT-OARSI responders are a proportion of responders and difference is reported as odds ratio (OR; 95% CI). AUSCAN function subscale scores were rescaled from 0–90 to 0–100 for calculation of OMERACT-OARSI responders.

Table 2: Change from baseline in primary and secondary outcomes at week 12 in the intention-to-treat population
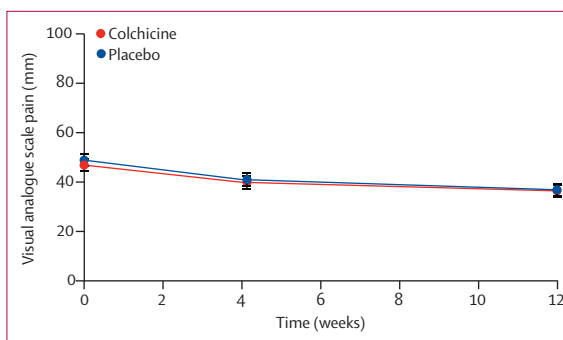

Figure 2: Visual analogue scale that reported pain in the fingers in the target hand for the intention-to-treat population
Data are least squares means with SEs over the entire study period.

	Colchicine (n=50)	Placebo (n=50)
Exposure time (participant weeks)	580	579
Adverse events		
Patients with adverse events	36 (72%)	22 (44%)
Number of adverse events (rate–events per participant week)	76 (0·13)	42 (0·07)
Adverse events leading to discontinuation	0 (0%)	0 (0%)
Maximum severity of adverse events in each patient*		
Mild	31 (62%)	16 (32%)
Moderate	4 (8%)	5 (10%)
Severe	1 (2%)	1 (2%)
Relationship to trial treatment (number of events [rate–events per participant week])		
Not related	28 (0·05)	19 (0·03)
Probably not related	3 (0·01)	5 (0·01)
Probably related	45 (0·08)	18 (0·03)
Classification (number of events [rate–events per participant week])		
General disorders†	4 (0·01)	2 (0·00)
Gastrointestinal disorders	24 (0·04)	14 (0·02)
Infections	8 (0·01)	6 (0·01)
Musculoskeletal disorders	8 (0·01)	5 (0·01)
Cardiac disorders	2 (0·00)	2 (0·00)
Neurological disorders	1 (0·00)	1 (0·00)
Urogenital disorders	3 (0·01)	0 (0·00)
Bone metabolism disorders	1 (0·00)	2 (0·00)
Alanine aminotransferase (>70 U/L for men and >45 U/L for women)	10 (0·02)	1 (0·00)
Estimated glomerular filtration rate (<60 mL/min per 1·73m²)	2 (0·00)	1 (0·00)
Creatine kinase (>280 U/L for men and >210 U/L for women)	8 (0·01)	2 (0·00)
Abnormal white blood count	1 (0·00)	2 (0·00)
Other‡	4 (0·01)	4 (0·01)
Serious adverse events		
Patients with serious adverse events	1 (2%)	1 (2%)
Number of events (rate–events per participant week)	1 (0·00)	2 (0·00)
Events leading to discontinuation	0 (0%)	0 (0%)
Relationship to trial treatment (number of events [rate–events per participant week])	0 (0·00)	0 (0·00)
Not related	1 (0·00)	0 (0·00)
Probably not related	0 (0·00)	2 (0·00)
Probably related	0 (0·00)	0 (0·00)
Death	0 (0%)	0 (0%)

Data are n (%), unless otherwise stated. *For each participant, the maximum severity experienced of each type of adverse event or serious adverse event is displayed. †General disorders include fatigue (one participant in the colchicine group, and one participant in the placebo group), dizziness (two participants in the colchicine group), general unease (one participant in the colchicine group) and headache (one participant in the placebo group). ‡Other include thrombophlebitis (one participant in the colchicine group), toothache (one participant in the colchicine group), teary eyes (one participant in the colchicine group), increased thirst (one participant in the colchicine group), cough (one participant in the placebo group), cataract (one participant in the placebo group), and dry skin (two participants in the placebo group).

Table 3: Adverse events in the safety population

primary outcome, secondary outcomes, and adverse events separated by sex are available in the appendix (pp 122–131).

Discussion

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

These results contradict our hypothesis that colchicine would be an effective drug for the pain associated with hand osteoarthritis, despite the fact that 87% of participants in our trial had inflammation in the fingers as assessed by ultrasound. A more potent anti-inflammatory drug, prednisolone, has been reported to be effective in reducing pain in people with inflammatory features of hand osteoarthritis at a dosage of 10 mg per day, but that trial included participants with inflammation evident on ultrasound who also experienced pain flares during a 48-h NSAID washout period prior to randomisation.[20]

Depositions of crystals, such as monosodium urate and calcium pyrophosphate crystals, in the joint mediate inflammation by inducing the maturation of interleukin-1β in an inflammasome-dependent manner. Stimulating cells with colchicine effectively blocks crystal-induced interleukin-1β maturation, which could be one explanation for the beneficial effects of colchicine in patients with gout and pseudogout.[22] We hypothesised that colchicine would be effective based on a proposed pathogenic role of crystals in osteoarthritis[6] although the involvement of crystals in osteoarthritis, in general, remains to be clarified.

Previous trials of colchicine for knee osteoarthritis have suggested a beneficial effect on pain, but overall estimates of efficacy from meta-analyses are uncertain with broad CIs.[11] Aside from the difference in osteoarthritis site, other differences in intervention and study populations could explain the discrepancy with our results. In one study showing effectiveness of colchicine, participants were treated with 1·5 mg colchicine per day for 6 months, and all participants had calcium pyrophosphate crystals verified by polarised light microscopy of the synovial fluid at inclusion, in addition to knee osteoarthritis.[23] Efficacy of colchicine in this setting thus supports the idea that colchicine is an effective therapy in crystal deposition diseases, but the generalisability of this finding is uncertain in relation to the overall osteoarthritis population, in which incidence of calcium pyrophosphate crystals in the joint is unknown. Similarly, 20 (56%) of 36 participants had radiographic chondrocalcinosis in another trial[24] in which colchicine was shown to be effective; and 29 (74%) of 39 participants had calcium pyrophosphate crystals in the

synovial fluid in another trial.[25] In both trials, colchicine was administered as an add-on therapy to NSAIDs[24] or an add-on to NSAIDs and intra-articular glucocorticoids.[25] Similar add-on strategies were also implemented in other trials showing benefit of colchicine for knee osteoarthritis, with colchicine combined with either NSAIDs or paracetamol.[11,12] The absence of efficacy of colchicine is now supported by two trials of colchicine 0·5 mg twice a day for 3 months for people with hand osteoarthritis and one trial of colchicine for 4 months for people with knee osteoarthritis.[9,26] Our study used the same intervention and comparator as applied in both of these studies. The study on knee osteoarthritis was longer in duration but had a comparable sample size, whereas the previous hand osteoarthritis trial is directly comparable with respect to study population, outcomes, and duration. The power in our trial was superior to the previous hand osteoarthritis trial, which included 32 patients in each group, with one participant lost to follow-up in each group. Our trial also included an extensive description of the study population regarding ultrasound inflammation, comorbidities, comedication, and analgesics, which was not addressed in the previous trial.[9] Both previous trials of colchicine showed higher numbers of adverse events in the colchicine group, driven primarily by gastrointestinal complaints compared with placebo groups.[9,26]

Quality of life scores (based on EQ-5D) increased more in the colchicine group than in the placebo group in our study. However, the increase was less than half of the minimal clinically important difference of the EQ-5D for people with knee osteoarthritis, which suggests limited clinical relevance of this result.[27] Subgroup analysis suggested that colchicine was effective for people without radiographic erosions at baseline, but this could reflect a type 1 error and should be confirmed by other trials.

In clinical trials like this one, the use of an appropriate comparator (control) group is necessary to control for factors that might have influenced the measurement of outcomes and to accurately assess the true contextual response to a treatment. The placebo response observed in this trial is probably influenced by various factors, including the expectations and beliefs of the participants and the health-care providers, 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 in both groups (thus excluding the likelihood of an effective experimental intervention) constitutes both regression to the mean and a true contextual response due to clinical attention, which is effective per se. A strength of our study is the rigorous methodological design, as well as adequate power, and no loss to follow up, which makes type 2 errors less likely. In addition, the CIs for between-group difference estimates for both primary and secondary outcomes were well within the predefined minimally clinically relevant difference,[19,20] offering a precise estimate for the efficacy of colchicine and placebo treatment.

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 most participants in our trial had ultrasound inflammation, this is considered a minor limitation. Another limitation is the dose of colchicine; a larger dose might be needed to obtain an effect in hand osteoarthritis. However, 0·5 mg twice a day was chosen in our study to minimise the risk of treatment failures due to gastrointestinal adverse events. The study medication was over-encapsulated, and thus might have been identifiable. Returned study medication was intact, and we do not suspect that blinding was compromised; however, we did not directly assess the success 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 might have overlooked a small treatment benefit given that 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 recommended for osteoarthritis, it is often used for this indication. This off-label use was documented in a randomised controlled trial of people with hand osteoarthritis showing that 7 (9%) of 82 participants reported use of colchicine.[28] Clinically, our results should be used to deter off-label use of colchicine for people with hand osteoarthritis, as our data do not support efficacy of the drug. Future research should address whether a sub-population of people with hand osteoarthritis and crystals could benefit from treatment.

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

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