Evaluating the safety and short-term equivalence of colchicine versus prednisone in older patients with acute calcium pyrophosphate crystal arthritis (COLCHICORT): an open-label, multicentre, randomised trial

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Summary

Background Acute calcium pyrophosphate crystal arthritis causes intense joint pain mainly affecting older people. Because guidance and evidence remain scarce, management of this disease relies on expert opinion. We therefore aimed to compare the safety and short-term equivalence of low-dose colchicine with oral prednisone in older patients with acute calcium pyrophosphate crystal arthritis.

Methods We did an open-label, multicentre, randomised, trial (COLCHICORT) at six hospitals in Paris and northern France. We enrolled patients who were admitted to hospital who were 65 years or older and who presented with acute calcium pyrophosphate crystal arthritis with a symptom duration of less than 36 h. Diagnosis of calcium pyrophosphate crystal arthritis was made by the identification of calcium pyrophosphate crystals on synovial fluid analysis or typical clinical presentation (onset of joint pain and swelling). Key exclusion criteria included absence of calcium pyrophosphate crystals on synovial fluid analysis or a history of gout. Participants were randomly allocated (1:1), using a centralised electronic treatment group allocation module, to receive either colchicine 1·5 mg on day 1 and 1 mg on day 2 (ie, the colchicine group) or oral prednisone 30 mg on days 1 and 2 (ie, the prednisone group). The primary outcome was change in joint pain (measured by visual analogue scale [VAS] from 0 mm to 100 mm) at 24 h. Equivalence was determined whether the 95% CI of the between-group difference at 24 h was within the –13 mm to +13 mm margin in the per-protocol analysis. Adverse events were recorded using the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0). This trial is completed and is registered with ClinicalTrials.gov, NCT03128905.

Findings Between Feb 5, 2018, and May 7, 2022, 111 patients who were admitted to hospital were randomly assigned (57 [51%] to the colchicine group and 54 [49%] to the prednisone group). 95 (86%) of 111 patients were included in the per-protocol analysis (49 [52%] in the colchicine group and 46 [48%] in the prednisone group). The median age was 88·0 years (IQR 82·0–91·0) and 69 (73%) of 95 participants were women and 26 (27%) were men. Acute calcium pyrophosphate crystal arthritis affected mainly the knee in 46 (48%) of 95 participants, the wrist in 19 (20%), and the ankle in 12 (13%). Pain VAS at baseline was 68 mm (SD 17). At 24 h, change in pain VAS was –36 mm (SD 32) in the colchicine group and –38 mm (SD 23) in the prednisone group. The between-group difference in change in pain VAS at 24 h was –1 mm (95% CI –12 to 10), showing equivalence between the two drugs. In the colchicine group, 12 (22%) of 55 patients had diarrhoea, one (2%) had hypertension, and none had hyperglycaemia. In the prednisone group, three (6%) of 54 had diarrhoea, six (11%) had hypertension, and three (6%) had hyperglycaemia. No deaths occurred in the colchicine group; two deaths occurred in the prednisone group, which were deemed unrelated to prednisone (one due to infectious valvular endocarditis leading to heart failure, and one due to a stroke).

Interpretation Colchicine and prednisone exhibit equivalent short-term efficacy for the treatment of acute calcium pyrophosphate crystal arthritis, with different safety profiles in the older population.

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Introduction

Calcium pyrophosphate deposition disease is the umbrella term for acute and chronic clinical manifestations induced by the presence of calcium pyrophosphate crystals inside and outside joints. This disease mainly occurs in the older population.[1,2] Acute calcium pyrophosphate crystal arthritis used to be referred to as pseudogout because of a clinical presentation resembling gout flares, with a distribution pattern usually affecting the knees and wrists rather than

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Research in context

Evidence before this study

Acute calcium pyrophosphate crystal arthritis causes intense joint pain and frequently occurs in older patients during hospital stays. In a search performed in 2018 for a white paper of unmet needs published by experts in the field, no randomised controlled trial testing any drug used for the management of acute calcium pyrophosphate crystal arthritis was found in the literature. On the basis of expert opinion and data extrapolated from gout studies, treatment of acute calcium pyrophosphate arthritis mainly relies on corticosteroids and oral colchicine, without any clear guidance to choose one or the other.

Added value of this study

2-day treatment regimens using oral colchicine or prednisone showed equivalent efficacy in controlling joint pain caused by acute calcium pyrophosphate crystal arthritis in older patients. Two-thirds of patients treated with colchicine or prednisone were considered good responders on day 3. We found that colchicine safety was marked by the onset of diarrhoea in more than one in five patients, and rare episodes of hypertension and hyperglycaemia occurred in patients treated with prednisone.

Implications of all the available evidence

Both oral colchicine and prednisone showed rapid pain relief in patients with acute calcium pyrophosphate crystal arthritis, without significant differences in efficacy. Choice between the two drugs should be guided by comorbid conditions, and given the substantial risk of induced diarrhoea with colchicine, the use of prednisone should be favoured in the absence of specific contraindications.

the foot. Similar to other crystal-related arthropathies, acute calcium pyrophosphate crystal arthritis is characterised by a rapid-onset inflammation of the joint causing very intense pain. Comparable with gout flares, a key management objective for acute calcium pyrophosphate crystal arthritis is rapid pain relief through the control of inflammation, which if untreated resolves in several days.[1] Acute calcium pyrophosphate crystal arthritis can require in-hospital management, but is mostly a common feature occurring during hospital stays of older patients for other reasons in medical and surgical wards, and has recently been associated with elevated short-term and long-term risk for non-fatal cardiovascular events.[3–5]

Despite the high frequency of the disease, no trials have assessed the efficacy of anti-inflammatory drugs for the treatment of acute calcium pyrophosphate crystal arthritis.[6–8] Inflammation in gout and calcium pyrophosphate deposition disease share similar pathophysiological pathways, as both monosodium urate and calcium pyrophosphate crystals strongly activate the NLRP3 inflammasome.[9] Thus, treatment of acute calcium pyrophosphate crystal arthritis mainly relies on expert opinion and data extrapolated from studies on the treatment of gout flares.[1,10–12] To control calcium pyrophosphate crystal-induced inflammation, the European Alliance of Associations for Rheumatology (EULAR) has recommended joint aspiration and steroid injection of the involved joint or the use of colchicine or steroids orally, stressing the need for appropriate clinical trials to support this approach.[7]

Intra-articular steroid injections require confirmation of the aseptic nature of the acute arthritis, imposing a 48-h delay after aspiration for joint fluid culture, and are not widely available. Oral colchicine and corticosteroids are expected to provide the best balance between efficacy and potential side-effects in the older population most commonly affected with calcium pyrophosphate deposition disease, and no data are available to suggest the superiority of one or the other.[1,13] Rapidity of treatment administration after acute crystal arthritis onset, particularly of colchicine, within 12–36 h, is a key element for treatment efficacy demonstrated in gout flares.[12] Given the paucity of published data for calcium pyrophosphate deposition disease management, and the absence of evidence from head-to-head comparison studies between colchicine and corticosteroids even in gout—particularly in the specific population of older adults—guidance for the choice between the two drugs in the treatment of acute calcium pyrophosphate crystal arthritis is absent. Research evaluating the efficacy and safety of various drugs in calcium pyrophosphate crystal arthritis was deemed a high priority by experts in the field, and the task force involved in the 2011 EULAR recommendations for the management of calcium pyrophosphate deposition disease acknowledged that evidence was sparse and that clinical trials were needed.[7,8] In this study, we therefore aimed to compare the safety and short-term equivalence of low-dose oral colchicine with oral prednisone in older people with acute calcium pyrophosphate crystal arthritis.

Methods

Study design and participants

We did an open-label, multicentre, randomised, trial (COLCHICORT) at six hospitals in Paris and northern France. We enrolled patients who were admitted to hospital who were 65 years or older and who presented with acute calcium pyrophosphate crystal arthritis with a symptom duration of less than 36 h. Criteria required for inclusion were diagnosis of acute calcium pyrophosphate crystal arthritis defined by the identification of calcium pyrophosphate crystals on synovial fluid analysis or typical clinical presentation (onset of joint pain and swelling reached a maximum in <24 h) with evidence of

chondrocalcinosis of the target joint or wrist, knee, or C1–C2 ligamentum flavum on conventional radiography, ultrasound, or CT.[14–19] Eligible patients had pain intensity on a visual analogue scale (VAS) of 40 mm or more (out of 100 mm) of the most painful joint. Patients were recruited by physicians of any specialty in their department, and each diagnosis of acute calcium pyrophosphate crystal arthritis was confirmed by a rheumatologist.

Key exclusion criteria were the absence of calcium pyrophosphate crystals on synovial fluid analysis, history of gout or presence of monosodium urate crystals on synovial fluid analysis, cognitive decline (either severe known neurocognitive disorders or acute delirium) impairing patients' ability to provide informed consent and pain assessment, treatments with anti-inflammatory properties over the past 7 days (corticosteroids, colchicine, non-steroidal anti-inflammatory drugs [NSAIDs], and interleukin-1 blockers), ongoing treatment with opioids except codeine and tramadol, known hypersensitivity to colchicine or prednisone, known contraindications to colchicine (severely impaired liver function, stage 4 or worse kidney disease—ie, estimated glomerular filtration rate [eGFR] <30 mL/min per 1·73 m²), lactose or saccharose intolerance (colchicine excipients), treatment with macrolides, pristinamycin, ciclosporin, verapamil, protease inhibitors, telaprevir (strong CYP3A4 inhibitors[20]), known contraindications to prednisone (systolic blood pressure ≥160 mm Hg, uncontrolled diabetes, uncontrolled bacterial infection, immunosuppression, and uncontrolled psychosis).

The trial protocol was reviewed and approved by a French National institutional review board (CPP Nord-Ouest number 17/43, registration number 2016, ANSM number 170356A-21). All patients provided written informed consent to participate in the study, which was done in accordance with the tenets of the Declaration of Helsinki. The study complied with the MR001 reference methodology with regard to the French Data Protection Authority (National Commission on Informatics and Liberty).

Randomisation and masking

Randomisation was centralised by an electronic treatment group allocation module, based on a list pre-established by a computer program under the control of a biostatistician from the Research Department of Groupe Hospitalier de l'Institut Catholique de Lille. Participants were randomly allocated (1:1) to either the colchicine group or prednisone group. Randomisation was balanced by blocks of variable size ranging from two to eight, and stratified on whether arthrocentesis had been done. This was an open-label study design; participants and investigators were not masked to treatment allocation, but those analysing the data were masked.

Procedures

Participants were randomly allocated to receive either oral colchicine 1·5 mg (1 mg and then 0·5 mg 1 h later) on day 1 and then 1 mg on day 2, or oral prednisone 30 mg on days 1 and 2. All patients received 1 g paracetamol and 50 mg tramadol three times per day during the first 24 h (or codeine 30 mg three times per day in case of known intolerance to tramadol). Further analgesic prescriptions were at the discretion of investigators and recorded from days 2 to 8. After day 3, any treatment with anti-inflammatory properties could be prescribed by the investigator (oral colchicine, oral prednisone, NSAIDs, intra-articular corticosteroids, or anakinra) and recorded until day 8.

Patients were asked to express their resting pain level during assessment using the VAS. Patient pain VAS values were recorded by a physician investigator on day 1 (baseline), day 2 (24 h), and day 3 (48 h), by study nurses 8 h and 12 h after baseline, and then noted daily by the patient from days 4 to 8 and transmitted on day 8 to a research assistant. Blood samples were drawn on days 1 and 3; laboratory tests included blood count, eGFR, liver enzymes, C-reactive protein (CRP), prothrombin, and glycaemia (on day 1 and fasting glucose on day 3; appendix p 7). All demographic data were collected at inclusion and verified from medical records. Sex was self-reported, and ethnicity was not collected as per French regulations.

See Online for appendix

Outcomes

The primary outcome was change from baseline pain (as measured by the VAS from 0 to 100 mm) recorded on day 2 (24 h) for the most painful (ie, index) joint. Secondary outcomes were response to treatment defined by pain VAS improvement of more than 50% from baseline or a pain VAS of less than 40 mm out of 100 mm on day 2 (24 h) and day 3 (48 h), and at least minor VAS pain improvement (>20% from baseline) on day 2 (24 h).

Adverse events were assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0). All adverse events were recorded, with a specific focus on diarrhoea, abdominal pain, nausea, vomiting, agitation, anxiety, euphoria, sleeping disorders, high blood pressure (>140 mm Hg for systolic blood pressure and >90 mm Hg for diastolic blood pressure), decreased eGFR, and fasting glucose of more than 2 g/L. Adverse events were considered related to the study drug if the investigator considered causality as certain, probable, or unknown, whereas those considered unrelated were excluded. No changes to the protocol were made after trial commencement.

Statistical analysis

Sample size was calculated assuming that the between-group difference in pain VAS change and its 95% CI at 24 h would fall into the –13 mm to +13 mm margin, considering that this value has been shown to be the minimal clinically important detectable between-group

difference.[11,21,22] Using this assumption and an arbitrary SD of 20 (from SDs observed in the gout flare trial comparing prednisolone and naproxen[10]), 56 participants per group would provide 80% power to show equivalence between colchicine and prednisone, with a one-sided type 1 error of 0·025, 10% loss to follow-up, and one-to-one allocation ratio. The significance level was set at 5% ($p \leq 0 \cdot 05$).

The mean absolute changes of pain VAS from baseline (day 1) to each timepoint were calculated within each treatment group. The primary endpoint was the change in pain VAS on day 2. Equivalence was determined if the 95% CI was included within the equivalence margin defined a priori in the protocol by –13 mm to +13 mm.

Secondary endpoints including changes in pain VAS on day 3, the proportion of responders on days 2 and 3, of at least minor response on day 2, CRP concentration changes, treatment response according to joint involvement, and acute arthritis duration before inclusion, were compared between groups by the χ^2 test or Fisher's exact test for qualitative data and with Student's t test or Wilcoxon-Mann-Whitney test for quantitative data. Using prednisone treatment as the reference, risk ratios (RRs) and their 95% CIs of not achieving treatment response with colchicine were calculated.

Safety (ie, occurrence of adverse events) was compared between groups using the χ^2 test or Fisher's exact test according to the Cochran's rule applied to the safety population (ie, participants having received at least one dose of colchicine or prednisone, irrespectively of which had been allocated; whereas the modified intention-to-treat population received at least one dose of the experimental drug and were analysed according to their randomisation group). Adverse events occurring during the first 48 h and during the 8-day follow-up are presented separately. For adverse events with high occurrences (>10%), baseline characteristics of participants presenting with a specific adverse event were compared to those not presenting with the adverse events. eGFR and systolic and diastolic blood pressure changes on day 3 were compared between groups.

Group comparability was checked with Student's *t* test or Wilcoxon-Mann-Whitney test according to normality from Shapiro-Wilk test for quantitative data; Welch's correction was applied in the Student's *t* test in case of heteroscedasticity. χ^2 test or Fisher's exact test were used for qualitative data. Efficacy analyses were done on the per-protocol population, which comprised participants who received the full dose of the experimental drugs according to treatment allocation.[23] Qualitative variables were described as numbers and percentages for each response modality; quantitative variables were described as mean (SD). If protocol deviations exceeded 10%, a sensitivity analysis was planned between the per-protocol population and the modified intention-to-treat population to compare the results. The modified intention-to-treat population included all randomly allocated participants having received at least one dose of study drug. An additional post-hoc sensitivity analysis was done on the primary criterion to check the 95% CI against equivalence margins adjusting on joint aspiration in the per-protocol and modified intention-to-treat populations. In a post-hoc multiple linear regression model explaining the pain VAS change at 24 h, joint aspiration was considered as an explanatory variable. The regression conditions were checked graphically (normality and homoscedasticity). The group model coefficient and its 95% CI were compared to raw pain VAS change difference between groups and its 95% CI. We did all statistical analyses using R (version 4.0.5).

This trial is completed and is registered with ClinicalTrials.gov, NCT03128905.

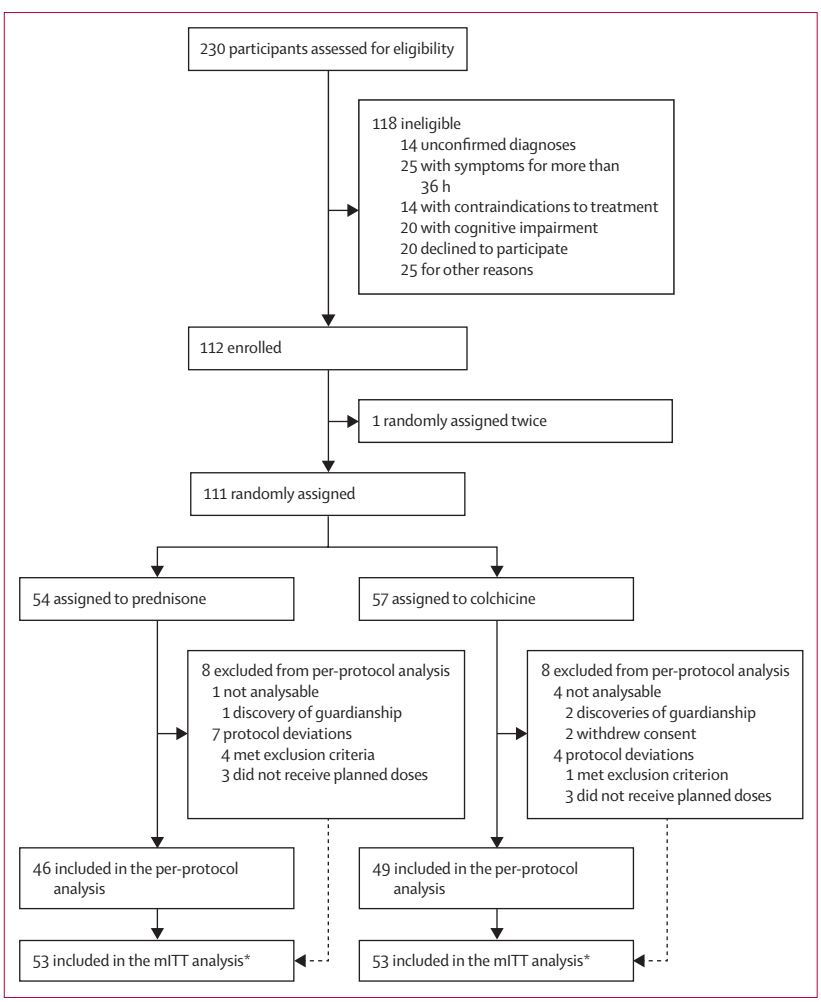

Figure 1: Trial profile
mITT=modified intention-to-treat. *Participants who had protocol deviations and received at least one allocated treatment dose were included in the mITT analysis.

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 Feb 5, 2018, and May 7, 2022, a total of 230 patients were screened, of whom, 111 (48%) were randomly assigned (57 [51%] to the colchicine group and 54 [49%] to the prednisone group). 95 (86%) of 111 participants were in the per-protocol population (49 [52%] in the colchicine group and 46 [48%] in the prednisone group). 106 (95%) of 111 participants were in the modified intention-to-treat population for the sensitivity analysis, and 109 (98%) were in the safety analysis population (figure 1). In the per-protocol population, the median age was 88·0 years (IQR 82·0–91·0), 69 (73%) of 95 participants were women and 26 (27%) were men, 24 (25%) had diabetes, 76 (80%) had hypertension, and median eGFR was 62·1 mL/min per 1·73 m² (IQR 45·2–81·5). Acute calcium pyrophosphate crystal arthritis with a first-ever flare was reported in 70 (74%) of 95 participants, crystal-proven synovial fluid analysis was reported in 39 (41%). Acute calcium pyrophosphate crystal arthritis affected mainly the knee in 46 (48%) participants, the wrist in 19 (20%), and the ankle in 12 (13%; table 1). The mean pain VAS at baseline was 68 mm (SD 17). None of the baseline characteristics differed substantially between groups except for sex. Causes of acute hospital admission are reported in the appendix (p 1).

On day 2 (24 h), change in pain VAS was –36 mm (SD 32) in the colchicine group and –38 mm (SD 23) in the prednisone group. The difference in change in pain VAS between the colchicine and prednisone groups was –1 mm (SD 6; 95% CI –12 to 10) showing equivalence between the two drugs. In the sensitivity analysis using the modified intention-to-treat population (n=106), the difference in change in pain VAS between the colchicine and prednisone groups was –4 mm (SD 5; 95% CI –15 to 7), which was partly outside the equivalence margin of –13 mm to +13 mm, showing uncertainty (figure 2). When adjusted on joint aspiration, the difference between groups was similar in the per-protocol population (–1 mm [SD 6; 95% CI –13 to 10]); the 95% CI again fell into the equivalence margin of –13 mm to +13 mm. In the modified intention-to-treat population, after adjustment on joint aspiration, the group model coefficient was –4 mm (SD 5; 95% CI –15 to 7).

A minor response on pain VAS (>20% improvement) was seen in 37 (76%) of 49 participants in the colchicine group and 41 (89%) of 46 in the prednisone group (p=0·25). Improvement in pain was similar between the two groups throughout the 2 days of protocolised treatments (figure 3A), and throughout the following 5 days of follow-up (appendix p 8). Among patients with a pain VAS of less than 40 mm at 48 h, 15 (25%) of 60 participants (nine [29%] of 31 in the prednisone group and six [21%] of 29 in the colchicine group; p=0·73) reported at least one daily pain VAS of more than 40 mm between days 3 and 8. Intra-articular corticosteroid

	Prednisone group (n=46)	Colchicine group (n=49)
Demographics		
Age, years	87·5 (84·2–91)	88 (79–91)
Sex		
Female	36 (78%)	33 (67%)
Male	10 (22%)	16 (33%)
BMI, kg/m²	24·8 (21–29·6)	25·2 (22·6–28·7)
Systolic blood pressure, mm Hg	129·9 (16·7)	131·1 (15·6)
Diastolic blood pressure, mm Hg	68·2 (16·9)	69·4 (13·6)
Characteristics of calcium pyrophosphate crystal arthritis		
Most painful (index) joint		
Shoulder	1 (2%)	5 (10%)
Elbow	2 (4%)	0
Wrist	12 (26%)	7 (14%)
Knee	22 (48%)	24 (49%)
Ankle	6 (13%)	6 (12%)
Cervical spine	1 (2%)	4 (8%)
Metacarpophalangeal joint	1 (2%)	2 (4%)
Other	1 (2%)	1 (2%)
Pain visual analogue scale value, mm	69·0 (17·8)	66·2 (17·2)
Calcium pyrophosphate crystals on synovial fluid analysis	20 (43%)	19 (39%)
Chondrocalcinosis on imaging	42/45 (93%)	42/44 (95%)
Osteoarthritis of the affected joint	22/42 (52%)	29/42 (69%)
Previous acute calcium pyrophosphate crystal arthritis	13 (28%)	12 (24%)
Comorbidities		
Hypertension	36 (78%)	40 (82%)
Diabetes	12 (26%)	12 (24%)
Dyslipidaemia	22 (48%)	22 (45%)
Ongoing treatments		
Statins	13 (28%)	15 (31%)
Antibiotics	8 (17%)	9 (18%)
Antihypertensives	39 (85%)	39 (80%)
Insulin	6 (13%)	9 (18%)
Oral antidiabetics	8 (17%)	8 (16%)
Antiemetics	2 (4%)	2 (4%)
Laxatives	14 (30%)	14 (29%)
Anti-diarrhoeal drug	0	1 (2%)
Biology		
Glycaemia, g/L	1·2 (1·1–1·4)	1·3 (1–1·5)
Estimated glomerular filtration rate, mL/min per 1·73 m²	57·3 (43·5–76·7)	69·7 (46·6–86)
C-reactive protein, mg/L	100 (41–166)	72 (36–121)

Data are median (IQR), mean (SD), or n (%).

Table 1: **Baseline characteristics of participants included in the per-protocol population**

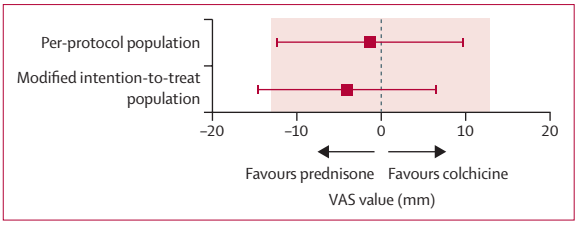

***Figure 2*: Forest plot for equivalence of prednisone versus colchicine for the treatment of acute calcium pyrophosphate arthritis**
Between-group difference in change in pain VAS at 24 h in the per-protocol population and in the modified intention-to-treat population (sensitivity analysis). Error bars are 95% CIs. The shaded area represents the –13 mm to +13 mm margin. VAS=visual analogue scale.

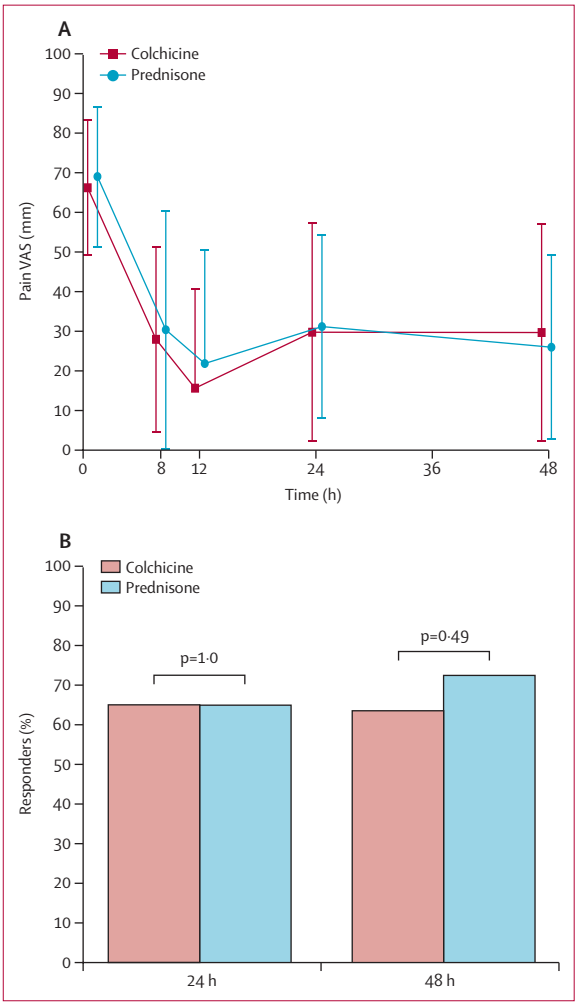

***Figure 3*: Pain and treatment response during the first 48 h of treatment of acute calcium pyrophosphate crystal arthritis**
(A) Pain VAS of patients treated with colchicine and prednisone during the first 48 h of follow-up. Error bars are SDs. (B) Proportion of treatment responders defined by more than 50% VAS pain reduction or pain VAS value of less than 40 mm after 24 h (ie, day 2) and 48 h (ie, day 3) in the colchicine and prednisone groups. VAS=visual analogue scale.

injections were given to six (13%) of 46 participants in the prednisone group and eight (16%) of 49 in the colchicine group after day 3 (p=0·87). Analgesics and anti-inflammatory treatments delivered beyond the study protocol doses are presented in the appendix (p 2). At 24 h, 32 (65%) of 49 participants in the colchicine group were responders versus 30 (65%) of 46 in the prednisone group (p=1·0), and at 48 h 31 (63%) were responders in the colchicine group versus 34 (74%) in the prednisone group (p=0·49; figure 3B). Taking prednisone as the reference, the RR of patients treated with colchicine not reaching treatment response was 1·0 (95% CI 0·57–1·73) at 24 h and 1·33 (0·72–2·45) at 48 h. Median relative decrease of CRP concentrations on day 3 was –12 mg/L (IQR –36 to 9) in the colchicine group and –34 mg/L (–72 to –2) in the prednisone group (p=0·49). Treatment response according to joint involvement (knees *vs* all other joints) suggested a greater response to prednisone on other joints than on the knee (appendix p 3). Improved response to colchicine was observed when the drug was administered less than 12 h after arthritis onset (appendix p 4).

In the safety population, during the 7-day follow-up, 16 (29%) of 55 participants in the colchicine group and 18 (33%) of 54 in the prednisone group had a treatment-related adverse event (p=0·79; table 2). The most frequent adverse event in the colchicine group was diarrhoea (12 [22%] of 55 *vs* three [6%] of 54 in the prednisone group); all but one adverse event was classified as mild and colchicine dose reduction to 0·5 mg on day 2 was required in one participant. Participants treated with colchicine who had diarrhoea (attributed or not to colchicine by investigators) were predominantly women (13 [87%] of 15 had onset of diarrhoea *vs* 25 [63%] of 40 had no onset of diarrhoea; p=0·11) and were treated more often with statins (seven [47%] of 15 *vs* nine [23%] of 40; p=0·10), but none of the candidate predictive factors (including age and eGFR) exhibited a significant association with diarrhoea (appendix p 5). The most frequent adverse events in the prednisone group were onset of hypertension (six [11%] of 54 *vs* one [2%] of 55 in the colchicine group; all mild), hyperglycaemia requiring insulin add-on therapy (three [6%] *vs* none in the colchicine group), and insomnia (two [4%] *vs* none in the colchicine group), all resolving and none of them requiring dose adjustment or discontinuation on day 2. All participants who had hypertension were women, but no potential predictive factor demonstrated a significant association with hypertension (appendix p 6). A general increase in systolic blood pressure was noted on day 3 in the prednisone group (mean increase of 8 mm Hg [SD 24] *vs* mean decrease of 1 mm Hg [18] in the colchicine group; p=0·062). Similarly, median fasting blood glucose concentrations on day 3 tended to be higher in the prednisone group than in the colchicine group (1·3 g/L [IQR 1·0–1·9] *vs* 1·1 g/L [0·9–1·3]; p=0·062). No significant change in eGFR was observed in either group. No deaths occurred in the colchicine group; two deaths occurred in the prednisone group. One (2%)

participant died 8 days after the first and only dose of prednisone. The death was deemed to be related to underlying infectious valvular endocarditis, which was diagnosed on day 2 of the study, and caused heart failure. One participant died suddenly on day 2; the death was suspected to have been due to a stroke. Both deaths were deemed unrelated to prednisone.

Discussion

In this study, done in patients with acute calcium pyrophosphate crystal arthritis, oral colchicine and oral prednisone were assessed as equivalent in terms of pain relief at 24 h. Both treatments were associated with infrequent but bothersome side-effects, particularly diarrhoea in patients treated with colchicine, which in clinical practice will require close monitoring and precautions in this older population.

To our knowledge, this study is the first randomised trial completed in people with acute calcium pyrophosphate crystal arthritis, and is the first head-to-head trial in calcium pyrophosphate deposition disease.[6,24,25] The only direct evidence of colchicine efficacy in acute calcium pyrophosphate crystal arthritis was for intravenous colchicine used in 17 patients, a route of administration that was abandoned more than two decades ago because of safety concerns.[26,27] Evidence also suggested that prophylactic use of oral colchicine can reduce the frequency of recurrence of acute calcium pyrophosphate crystal arthritis.[28] In gout flares, however, the randomised, placebo-controlled, double-blind clinical trial AGREE showed that low-dose (1·8 mg per day) and high-dose (4·8 mg per day) colchicine had similar short-term efficacy.[12] In the CONTACT trial, 1·5 mg per day colchicine also showed similar efficacy to NSAIDs in a head-to-head comparison with naproxen 750 mg per day for gout flares.[29] On the basis of these data gathered from patients with gout, and considering the similar pathophysiological pathways of inflammation in gout and calcium pyrophosphate crystal arthritis,[9] the loading dose of colchicine chosen for the COLCHICORT trial was 1·5 mg on day 1, as suggested by EULAR,[7] which is higher than the maximum regimen of 1 mg per day in Europe or 1·2 mg per day in the USA recently recommended by experts.[1] The evidence gathered on the use of corticosteroids for the treatment of acute calcium pyrophosphate crystal arthritis is scarce, and no study has reported on the use of oral corticosteroids.[30] Evidence for corticosteroid efficacy in gout flares mostly relies on head-to-head comparisons of prednisolone 30 mg or 35 mg per day versus NSAIDs.[10,11] The pain relief response rates observed in both of our study groups would suggest that the colchicine and corticosteroid doses extrapolated from those used for gout flares were rightfully applied for assessing these drugs' effects in acute calcium pyrophosphate crystal arthritis. These results suggest that a 2-day regimen might be sufficient in two-thirds of patients (particularly for prednisone) without substantial relapses, and that when needed, treatment maintenance should be reassessed daily. Subgroup analyses on treatment response according to the type of joint involvement and time since onset of the acute arthritis were underpowered to detect a statistical difference. However, prednisone seemed to exhibit a more rapid response in smaller joints than in the knees. In addition, as previously shown in the AGREE trial in patients with gout, a window of opportunity of 12 h after onset for treatment with colchicine might exist for acute calcium pyrophosphate crystal arthritis.[12]

Although efficacy in relieving pain in acute calcium pyrophosphate crystal arthritis is equivalent between colchicine and prednisone, safety differed with the development of specific adverse events of each drug. The safety profile for colchicine was marked by gastrointestinal adverse events; more than a fifth of patients had diarrhoea, which required dose reduction as soon as day 2 in one patient. This proportion was similar to the incidence of diarrhoea in the low-dose colchicine group of the AGREE trial. Because diarrhoea can lead to dehydration in older people, this side-effect is important to take into account when considering the use of colchicine.[12] Although age and renal impairment did not seem to predict the occurrence of diarrhoea, ongoing treatment with statins (which, similar to colchicine, are competitively metabolised by cytochrome P450 3A4 or constitute a P-glycoprotein substrate),[31,32] tended to be more frequent in patients treated with colchicine who developed diarrhoea. The statistical power of our study was, however, insufficient to provide a formal comparison. These results further underline the need to consider co-prescriptions, especially commonly prescribed statins,

	Prednisone (n=54)	Colchicine (n=55)
Diarrhoea	3 (6%)	12 (22%)
Nausea	1 (2%)	3 (5%)
Vomiting	1 (2%)	0
Abdominal pain	0	2 (4%)
Excitation	2 (4%)	0
Anxiety	1 (2%)	1 (2%)
Euphoria	1 (2%)	0
Insomnia	2 (4%)	0
Hyperglycaemia	3 (6%)	0
Hypertension	6 (11%)	1 (2%)
Heart failure	1 (2%)	1 (2%)
Delirium	1 (2%)	0
Serious infection	1 (2%)	0
Other	3 (6%)	2 (4%)

Data are n (%).

***Table 2*: Occurrence of adverse events related to prednisone and colchicine during the 7-day follow-up in the safety population**

before administrating colchicine in patients with acute calcium pyrophosphate crystal arthritis.[20] Further research is warranted to identify factors predictive of the onset of adverse events, particularly diarrhoea, when using colchicine in the treatment of calcium pyrophosphate crystal arthritis. Our prednisone tolerance data were reassuring, with six (11%) of 54 patients having induced hypertension (a modest increase in systolic blood pressure on day 3) and only three (6%) had increased fasting glucose concentrations, none of whom seemed to present any associated predictive factors. Most patients with diabetes did not have any change in their blood glucose concentration after this 2-day regimen.

Our study has limitations. First, we did not include a placebo group, which in the context of the variable natural history of acute calcium pyrophosphate crystal arthritis makes it difficult to determine the effect size of the two drugs for pain relief. Yet, given that patients affected with acute calcium pyrophosphate crystal arthritis experience intense pain (which in the case of older patients can be responsible for complications beyond discomfort), we considered that a placebo group would have been unethical, because even if direct evidence was scarce, extrapolated results from trials of gout flares have produced sufficiently convincing evidence that available therapeutic options provide substantial pain relief. Pain intensity of crystal-related arthritis and the risk of under-treating acute pain in older adults[33] also motivated the standardised analgesic procedure for all patients who participated. This regimen promoted rapid pain control in the first hours of treatment, and contributed to the high numbers of treatment responders as soon as day 2. We expect the standardisation of the analgesic procedure until the primary outcome measure to have limited the bias induced the use of analgesics. Second, NSAIDs have been suggested as the potential second-line systemic treatment after colchicine,[1] but their use is unsafe in a vast majority of patients older than 65 years[34] as underlined by the 2011 EULAR taskforce,[7] explaining why an NSAID group was not included in the trial. Third, treatment allocation was not masked, which might have biased assessments. However, as most patients were having a first flare, with no previous experience or knowledge concerning the interventional drugs, and as the primary endpoint (pain VAS) did not involve the investigator's assessment, we believe that the open-label nature of the study did not have a substantial effect on the primary outcome assessment. Fourth, more than the expected 10% of participants were excluded from the per-protocol analysis, which still allowed equivalence between the drugs to be demonstrated, but might be limited by some selection bias. A sensitivity analysis was done on the modified intention-to-treat population. This population included all patients except those under guardianship (n=5), which therefore limited selection bias with some measurement bias. Equivalence was not shown in this sensitivity analysis, which nuanced the study results, as a slight superiority of prednisone could not be ruled out. Finally, the median age of participants was uncommonly high for a clinical trial. This finding might have produced a selection bias due to cognitive impairment-related screening failures, but accurately represented the population affected with acute calcium pyrophosphate crystal arthritis. We would like to highlight that the study population comprised patients admitted to hospital, with the potential limitation of generalisability to all patients with acute calcium pyrophosphate crystal arthritis, particularly for those treated in primary care.

In conclusion, this study is the first randomised trial in patients with acute calcium pyrophosphate crystal arthritis. We demonstrated short-term efficacy equivalence between two 2-day regimens: low-dose colchicine and oral prednisone. The choice between the two drugs should be guided by safety considerations. Because of the substantial risk of induced diarrhoea with colchicine, prednisone in the absence of specific contraindications should be favoured.

Contributors

TP, EH, VD, LN, PR, and TB conceived and designed the study. LN oversaw development of the trial database and randomisation procedure. TP, PR, SO, RL, NS, AP, AG, HL, TR, XD, PM, FV, AM, NB, SM, PR, and VD recruited participants, provided the care, and did the data collection. AL organised drug delivery. J-FB organised baseline imaging procedures. TP and LN accessed and verified the data underlying the study. LN did the statistical analysis. TP, LN, PR, TB, and EH did the clinical data analysis and interpretation. TP wrote the first draft of the report with input from PR, TB, EH, and LN. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

We declare no competing interest.

Data sharing

Deidentified patients' data can be requested by researchers for use in independent scientific research and will be provided following review and approval of the research proposal (including statistical analysis plan) and completion of a data sharing agreement with the Lille Catholic University Hospitals. Data requests can be made anytime from 9 months after the publication of this trial for up to 5 years (extendable). Requests should be sent to the corresponding author.

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