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Inflammation as a target for treatment in hand osteoarthritis

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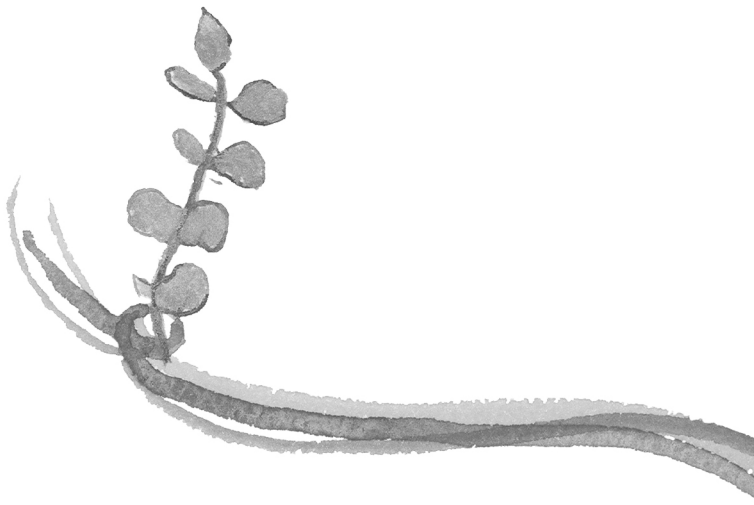
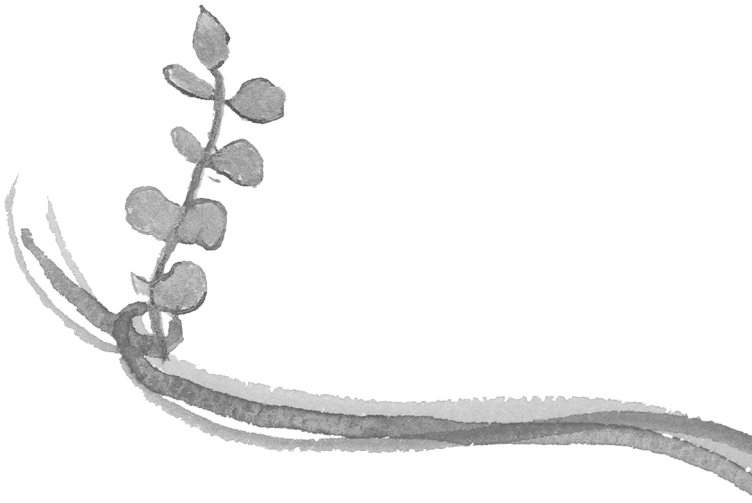
PART II

Inflammation as treatment target



CHAPTER 5

Results of a 6-week treatment with 10 mg prednisolone in patients with hand osteoarthritis (HOPE): a double-blind, randomised, placebo-controlled trial



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SUMMARY

Background. Hand osteoarthritis is a prevalent joint condition that has a high burden of disease and an unmet medical need for effective therapeutic options. Since local inflammation is recognized as contributing to osteoarthritic complaints, the Hand Osteoarthritis Prednisolone Efficacy (HOPE) study aimed to investigate the efficacy and safety of short-term prednisolone in patients with painful hand osteoarthritis and synovial inflammation.

Methods. The HOPE study is a double-blind, randomised, placebo-controlled trial. We recruited eligible adults from rheumatology outpatient clinics at two sites in the Netherlands. Patients were considered eligible if they had symptomatic hand osteoarthritis and signs of inflammation in their distal and proximal interphalangeal (DIP/PIP) joints. For inclusion, patients were required to have four or more DIP/PIP joints with osteoarthritic nodes; at least one DIP/PIP joint with soft swelling or erythema; at least one DIP/PIP joint with a positive power Doppler signal or synovial thickening of at least grade 2 on ultrasound; and finger pain of at least 30 mm on a 100-mm visual analogue scale (VAS) that flared up during a 48-h non-steroidal anti-inflammatory drug (NSAID) washout (defined as worsening of finger pain by at least 20 mm on the VAS). Eligible patients were randomly assigned (1:1) to receive 10 mg prednisolone or placebo orally once daily for 6 weeks, followed by a 2-week tapering scheme, and a 6-week follow-up without study medication. The patients and study team were masked to treatment assignment. The primary endpoint was finger pain, assessed on a VAS, at 6 weeks in participants who had been randomly assigned to groups and attended the baseline visit. This study is registered with the Netherlands Trial Registry, number NTR5263.

Findings. We screened patients for enrolment between Dec 3, 2015, and May 31, 2018. Patients completed baseline visits and started treatment between Dec 14, 2015, and July 2, 2018, and the last study visit of the last patient was Oct 4, 2018. Of 149 patients assessed for eligibility, 57 (38%) patients were excluded (predominantly because they did not meet one or several inclusion criteria, most often because of an absence of synovial inflammation or of flare-ups after NSAID washout) and 92 (62%) patients were eligible for inclusion. We randomly assigned 46 (50%) patients to receive prednisolone and 46 (50%) patients to receive placebo, all of whom were included in the modified intention-to-treat analysis of the primary endpoint. 42 (91%) patients in the prednisolone group and 42 (91%) in the placebo group completed the 14-week study. The mean change between baseline and week 6 on VAS-reported finger pain was -21.5 (SD 21.7) in the prednisolone group and -5.2 (24.3) in the placebo group, with a mean between-group difference (of prednisolone *vs* placebo) of -16.5 (95% CI -26.1 to -6.9; p=0.0007). The number of non-serious adverse events was similar between the groups. Five serious adverse events were reported during our study: one serious adverse event in the prednisolone group (a myocardial infarction) and four serious adverse events in the placebo group (an infected traumatic leg haematoma that required surgery, bowel surgery, atrial fibrillation that required a pacemaker implantation,

and symptomatic uterine myomas that required a hysterectomy). Four (4%) patients discontinued the study because of an adverse event: one (2%) patient receiving prednisolone (for a myocardial infarction) and three (7%) patients receiving placebo (for surgery of the bowel and for an infected leg haematoma and for Lyme disease arthritis of the knee).

Interpretation. Treatment with 10 mg prednisolone for 6 weeks is efficacious and safe for the treatment of patients with painful hand osteoarthritis and signs of inflammation. The results of our study provide clinicians with a new short-term treatment option for patients with hand osteoarthritis who report a flare-up of their disease.

Funding. Dutch Arthritis Society.

INTRODUCTION

Around 20% of adults have osteoarthritis.[1,2] A particularly burdensome manifestation is hand osteoarthritis, which is found in 8-10% of the adult general population. The prevalence of hand osteoarthritis is 26% in women older than 70 years, and the estimated lifetime risk of the disease in the general population is 40%.[2-4] A substantial burden of disease is associated with hand osteoarthritis, since the condition presents with hand pain, disability, and reduced quality of life, for which patients frequently consult health-care providers.[3,5,6] Symptoms in the hands usually fluctuate over time, including episodes of joint swelling and erythema.[7]

There are several therapeutic options for patients with painful hand osteoarthritis, which vary from non-pharmacological approaches, such as education and exercise, to analgesics, but their effects are modest. Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used for symptom relief, yet their effect is moderate at best and safety aspects restrict their use, especially in older people (those older than 65 years).[8-10] Therefore, there is an unmet need for effective therapies for hand osteoarthritis.

The current treatment approach relates to the traditional idea that osteoarthritis is a degenerative disease characterised by cartilage loss and bone deformations. Accumulating evidence from the past decade suggests that osteoarthritis is a disease involving all joint compartments, in which not only mechanical triggers but also local inflammation cause pain and radiographical damage progression.[1,11-16] Therefore, inflammation is a potential treatment target in osteoarthritis.

Glucocorticoids are potent multitargeted anti-inflammatory drugs, and we therefore hypothesised that signs and symptoms in patients with hand osteoarthritis would improve by suppressing local inflammation with glucocorticoids.

We aimed to investigate the clinical efficacy and safety of short-term treatment with the glucocorticoid prednisolone in patients with painful hand osteoarthritis who had evidence of synovial inflammation.

METHODS

Study design and patients

The Hand Osteoarthritis Prednisolone Efficacy (HOPE) study is a double-blind, randomised, placebo-controlled trial. We recruited eligible adults from rheumatology outpatient clinics at two sites in the Netherlands (appendix p 1). Patients were considered eligible if they had symptomatic hand osteoarthritis that fulfilled the American College of Rheumatology criteria[11] and if they had signs of inflammation in their distal and proximal interphalangeal (DIP/PIP) joints. For inclusion, patients were required to have four or more DIP/PIP joints with osteoarthritic nodes; at least one DIP/PIP joint with soft swelling or erythema; at least one DIP/PIP joint with a positive power Doppler signal (PDS) or synovial thickening of at least grade 2 on ultrasound; and finger pain of at least 30 mm on a 100-mm visual analogue scale (VAS) that flared up during

a 48-h NSAID washout (defined as worsening of finger pain by at least 20 mm on the VAS). In patients with NSAID contraindications, flare-ups were assessed by use of paracetamol. We excluded patients who predominantly had pain in their thumb base rather than digital pain. FPBK screened all patients.

Because of slow accrual during the trial, we decided to also include patients who did not have a flare-up during a 48-h NSAID washout but who fulfilled all other inclusion criteria and more stringent pain (VAS ≥40 mm) and ultrasound criteria (positive PDS). This decision was supported by a systematic literature review[12] of 57 trials, which showed that osteoarthritis trials using a study design without flare-up inclusion criteria did not have altered effect sizes relative to those with this criterion.

We excluded patients who had used immune-modulating drugs 90 days or fewer before baseline (eg, anti-malarials or systemic or local glucocorticoids), who were positive for rheumatoid factor or anti-cyclic citrullinated peptide antibodies, or who had chronic inflammatory rheumatic diseases, psoriasis, uncontrolled serious comorbidities, cancers, or infectious diseases, among several other exclusion criteria (appendix p 1).

Our study was approved by the medical ethics committees at Leiden University Medical Center and Zuyderland Medical Center, and it was conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki. All patients provided written informed consent. The study protocol is shown in the appendix (pp 11-46).

Randomisation and masking

We randomly assigned patients (1:1) to receive prednisolone or placebo by use of a block randomisation scheme with a fixed block size of six. The Leiden University Medical Center pharmacy generated the randomisation list and were not subsequently involved in the trial. Study medication (5 mg/mL oral prednisolone solution or placebo solution) was provided in sequentially numbered bottles. Prednisolone and placebo solutions were identical in appearance, smell, and taste. Patients, outcome assessors (not authors), and data analysts (FPBK and SB) remained masked for treatment allocation until the study database was locked.

Procedures

Patients self-administered 2 mL of 5 mg/mL prednisolone solution (ie, a 10 mg dose) or placebo once daily for 6 weeks. Thereafter, medication was tapered: patients self-administered 5 mg prednisolone or placebo for 1 week, followed by 2.5 mg prednisolone or placebo for 1 week. From weeks 9-14, study medication was stopped. Patients recorded their adherence to treatment in a diary.

Up to 3000 mg paracetamol per day was allowed as rescue medication. A stable dosage of chondroitin sulphate, glucosamine, bisphosphonate, tetracycline, or oestrogens were allowed, but NSAIDs and intramuscular or intra-articular glucocorticoid or hyaluronic acid injections were not. Patients were discouraged from starting new non-pharmacological interventions. Patients who were at risk of developing gastric or duodenal ulcers were prescribed a proton-pump inhibitor during the 8-week treatment period.

Trained nurses made clinical assessments at baseline and weeks 2, 6, and 14. At every study visit, the nurses recorded tenderness upon palpation (a score of 0-3 on the Doyle Index in the hand) and soft joint swelling (absent or present) for DIP/PIP joints 2-5, interphalangeal joint 1 (ie, of the thumb), metacarpophalangeal joints 1-5, and the first carpometacarpal joint. Nurses also assessed grip strength (in kg), physician global assessment of the patient by VAS, and rescue medication use. Telephone calls to confirm questionnaire completion and to check for any rescue medication use were made at weeks 4 and 8.

At baseline and weeks 2, 4, 6, 8, and 14, patients completed questionnaires, including a VAS of finger pain, the Australian-Canadian Hand Osteoarthritis Index, the Michigan Hand Outcomes questionnaire, the Functional Index for Hand Osteoarthritis, a VAS of thumb-base pain, a patient global assessment with VAS, a VAS of fatigue, and the Short Form-36 physical component scale. At week 6, patients were also asked which treatment they believed they had received.

Hand radiographs were taken at baseline, unless radiographs had been taken in the previous 6 months. Radiographic damage was assessed with the Kellgren-Lawrence system (a score of 0-4 in 30 joints).[13] Erosive osteoarthritis was defined as having at least one joint in Verbruggen-Veys erosive or remodelling phase.[14] Synovial thickening and PDS (scored as 0-3 in 30 joints)[15] were assessed on ultrasound at baseline and weeks 6 and 14. Contrast-enhanced MRI of DIP/PIP joints 2-5 was done at baseline and week 6 to assess synovitis (scored 0-3.5) and bone marrow lesions (0-3).[16] Details of questionnaires and imaging assessments are shown in the appendix (pp 2-6).

Outcomes

The primary endpoint was finger joint pain after 6 weeks on a 100-mm VAS, assessed in a modified intention-to-treat population (all participants randomly assigned to groups and who attended a baseline visit). Secondary clinical endpoints were finger pain at weeks 8 and 14; fulfilment of Outcome Measures in Rheumatology-Osteoarthritis Research Society International (OMERACT-OARSI) responder criteria (appendix pp 2-3)[17] at weeks 6 and 14; scores on the Australian-Canadian Hand Osteoarthritis Index pain (scored as 0-20) and function subscales (0-36), the Functional Index for Hand Osteoarthritis (0-30), an assessment of thumb-base pain (on VAS), a patient global assessment (on VAS), fatigue (on VAS), and a norm-based Short Form-36 physical and mental component scale at weeks 6, 8, and 14; and scores on the Michigan Hand Outcomes questionnaire pain and function subscales (scored as 0-100), a physician global assessment (on VAS), the Doyle Index of tender joints in the hand (scored as 0-90), a swollen joint count (0-30), and grip strength at weeks 6 and 14. Secondary imaging endpoints were synovial thickening and PDS by ultrasound (at weeks 6 and 14) and synovitis and bone marrow lesions by MRI (at week 6). Safety endpoints were the number of adverse events, serious adverse events, withdrawals because of adverse events, and changes in blood glucose concentrations between baseline and week 2. Secondary endpoints were assessed in the modified intention-to-treat population (all participants randomly assigned to groups and who attended a baseline visit).

We did a prespecified exploratory analysis of the primary endpoint (finger joint pain after 6 weeks on a 100-mm VAS) in the per-protocol population (all patients meeting the study entry criteria, with no major protocol violations, who completed the study). We also did a prespecified sensitivity analysis of the primary endpoint, in which we excluded patients who did not report a flare-up after analgesic washout.

Finally, we did a post-hoc subgroup analysis of the primary endpoint in patients with erosive osteoarthritis and a post-hoc analysis of the imaging endpoints at the patient level using sum scores (ie, by adding the scores of each individual joint, we generated a sum score per patient).

Statistical analysis

To detect a 15-mm between-group difference in finger joint pain by VAS after 6 weeks (primary outcome), with an SD of 22 for change from baseline and an α-level of 0.05, we required 35 participants per group to attain a power of 80% or 45 participants per group to attain a power of 90%. Accounting for an expected 10% loss to follow-up, we sought to include 90 patients.

We analysed all endpoints with generalised estimating equations, and we used robust standard errors and the working correlation structure specified as exchangeable. Data from all available timepoints were used. The independent variables included in our model were treatment group, visit number (categorical), interaction between treatment group and visit number, the baseline value of dependent variable (continuous), and study centre (categorical). We also ran a model that additionally adjusted for age and sex for the primary endpoint. We analysed imaging endpoints at a joint level to account for clustering of joints within patients.

The primary analysis was done with generalised estimating equations for the primary endpoint in the described modified intention-to-treat approach. Secondary endpoints were also analysed with this modified intention-to-treat approach.

We analysed data with Stata version 14. The statistical analysis plan, which was written before breaking the randomisation code, is shown in the appendix (pp 47-51). This study is registered with the Netherlands Trial Registry, number NTR5263.

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 patients for enrolment between Dec 3, 2015, and May 31, 2018. Patients completed baseline visits and started treatment between Dec 14, 2015, and July 2, 2018, and the last study visit of the last patient was Oct 4, 2018. Of 149 patients assessed for their eligibility, 57 (38%) patients were excluded (predominantly because they did not meet one or several inclusion criteria, most often because of an absence of synovial inflammation or of flare-ups after NSAID washout) and 92 (62%) patients were eligible for inclusion (figure 1).

We randomly assigned 46 (50%) patients to receive prednisolone and 46 (50%) patients to receive placebo, all of whom were included in the modified intention-to-treat analysis of the primary endpoint. 42 (91%) patients in the prednisolone group and 42 (91%) in the placebo group completed the 14-week study. The remainder of the participants discontinued participation before this time, including two patients in the prednisolone group (one for poor efficacy and one for a myocardial infarction) and four patients in the placebo group (three with adverse events and one who withdrew consent) who withdrew from the study before the 6-week assessment. Baseline characteristics were well balanced between the groups (table 1).

Table 1. Baseline characteristics of study participants.

	Prednisolone (n=46)	**Placebo (n=46)**
Age, years	62.2 (8.8)	65.6 (8.5)
Sex		
Female	38 (83%)	35 (76%)
Male	8 (17%)	11 (24%)
Body mass index, kg/m^2	26.9 (4.4)	27.2 (4.9)
Disease duration, years	6.9 (7.7)	6.2 (9.0)
Erosive osteoarthritis*	34 (74%)	33 (72%)
Kellgren-Lawrence sum score, 0-120	35.3 (15.4)	39.5 (16.1)
VAS score of pain in fingers, 0-100	54.4 (21.8)	53.6 (19.3)

Data are mean (SD) or n (%). VAS=visual analogue scale. *Defined as a joint in Verbruggen-Veys erosive or remodeling phase.

All patients reported adherence to the study medication of more than 80% in their diary. At week 6, 65 (76%) patients (36 patients in the prednisolone group and 29 patients in the placebo group) agreed to guess their treatment group assignment, of whom 27 patients in each group guessed correctly and nine patients in the prednisolone group and two patients in the placebo group guessed incorrectly. At week 6, nine (20%) of 44 patients in the prednisolone group versus 16 (38%) of 42 patients in the placebo group reported frequent paracetamol use (twice per week or more) as rescue medication for hand complaints over the past 2 weeks (odds ratio for difference 0.43, 95% CI 0.16-1.13; p=0.085).

The mean change between baseline and week 6 on VAS-reported finger pain was -21.5 (SD 21.7) in the prednisolone group and -5.2 (24.3) in the placebo group (figure 2), with a mean between-group difference (of prednisolone vs placebo) of -16.5 (95% CI -26.1 to -6.9; p=0.0007). Adjustment for age and sex yielded similar results, showing a mean difference of -16.4 (-26.0 to -6.9; p=0.0008).

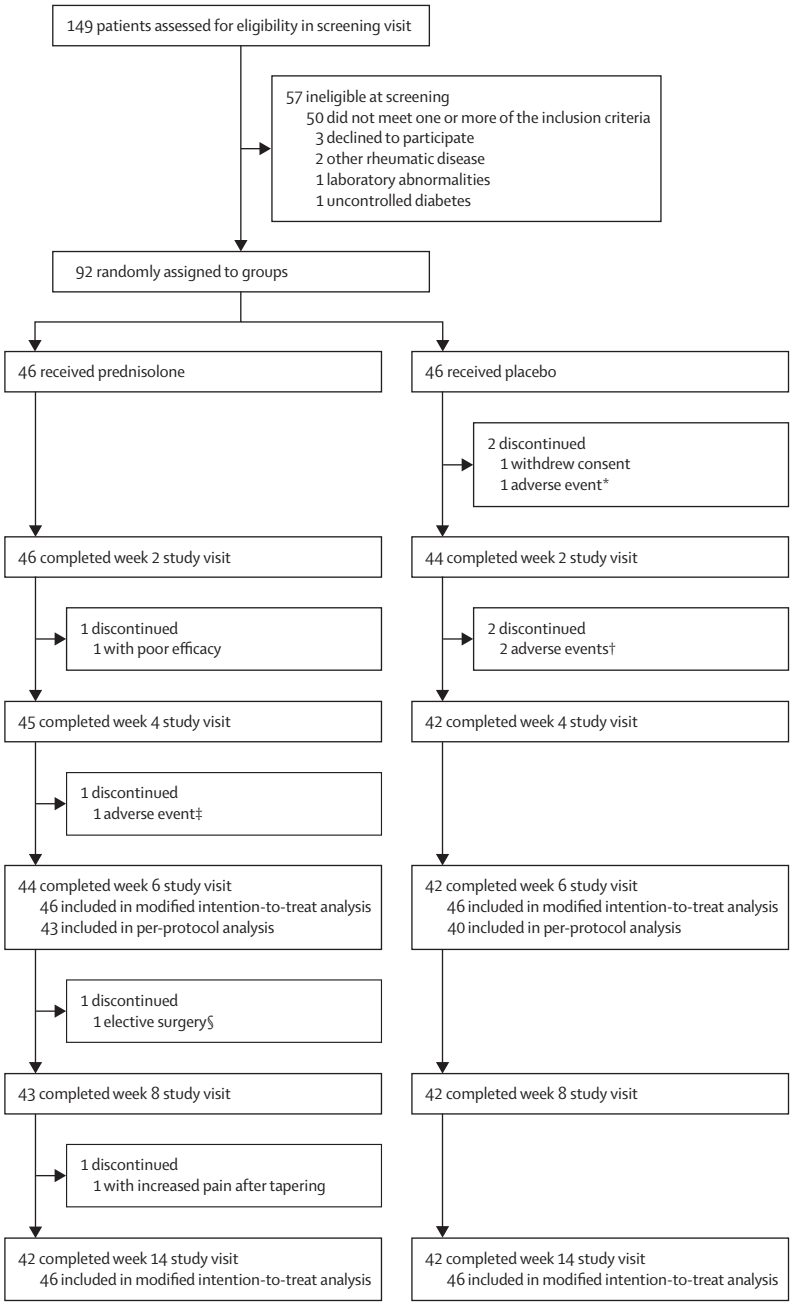

Figure 1. Trial profile.

*Bowel surgery (a serious adverse event). †Infected traumatic leg haematoma that required surgery (a serious adverse event) and Lyme disease arthritis of the knee (an adverse event). ‡Myocardial infarction (a serious adverse event). §An elective repair of a traumatic shoulder tendon rupture (for a trauma that occurred before the study started).

After study drug tapering, the between-group mean difference in VAS-recorded finger pain reduced to -8.5 (95% CI -18.5 to 1.5) at week 8 and 6.6 (-3.7 to 16.9) at week 14 (figure 2). At 6 weeks, 33 (72%) patients in the prednisolone group versus 15 (33%) patients in the placebo group fulfilled OMERACT-OARSI responder criteria. In most secondary endpoints concerning pain and function, prednisolone was superior to placebo at 6 weeks (table 2). Scores in the Short Form-36 physical component summary scale decreased more in patients treated with prednisolone than placebo, whereas no relevant difference in number of soft swollen joints was observed. No differences between the groups were seen for grip strength, fatigue on the VAS, or the Short Form-36 mental component summary scale (appendix p 7). In analogy with our findings on the primary endpoint, between-group differences for secondary endpoints were not sustained after study drug tapering (appendix p 8).

At week 6, the mean synovial thickening score per joint by ultrasound was lower in the prednisolone group than in the placebo group (mean difference -0.08, 95% CI -0.13 to -0.04; p=0.0004; table 2; figure 2). We did not observe a between-group difference in PDS score by ultrasound or synovitis score per joint by MRI (appendix p 9), whereas bone marrow lesions (assessed by MRI) appeared less severe in the prednisolone group (-0.04, -0.06 to -0.01; p=0.007). At week 14, the parameters assessed by ultrasound returned to baseline levels, and between-group differences disappeared (table 2; figure 2).

The number of non-serious adverse events was similar between the groups (43 events in 19 [41%] patients in the prednisolone group *vs* 43 adverse events in 19 [41%] patients in the placebo group; table 3). Five serious adverse events were reported during our study: one serious adverse event in the prednisolone group (a myocardial infarction) and four serious adverse events in the placebo group (an infected traumatic leg haematoma that required surgery, bowel surgery, atrial fibrillation that required a pacemaker implantation, and symptomatic uterine myomas that required a hysterectomy). Four (4%) patients discontinued the study because of an adverse event: one (2%) patient receiving prednisolone (for a myocardial infarction) and three (7%) patients receiving placebo (for surgery of the bowel and for an infected leg haematoma and for Lyme disease arthritis of the knee). The mean change between baseline and week 2 in blood glucose concentrations was 0.2 mmol/L (SD 1.2) in the prednisolone group and 0.4 mmol/L (1.5) in the placebo group. Hyperglycaemia occurred in one (2%) patient in the prednisolone group and three (7%) patients in the placebo group.

Analysis of the primary endpoint in the per-protocol population (43 patients in the prednisolone group and 40 patients in the placebo group) showed similar results as the primary analysis (mean between-group difference -15.1, 95% CI -24.9 to -5.2; p=0.0027), as did the sensitivity analysis, in which we excluded patients (13 patients in the prednisolone group and six patients in the placebo group) who did not have a flare-up after analgesic washout (-17.8, -28.5 to -7.1; p=0.0011), and a subgroup analysis in patients with erosive osteoarthritis only (-16.6, -28.1 to -5.2; p=0.0043). Post-hoc analysis of the imaging endpoints at the patient level using sum scores gave similar results to the joint-level analyses (table 2).

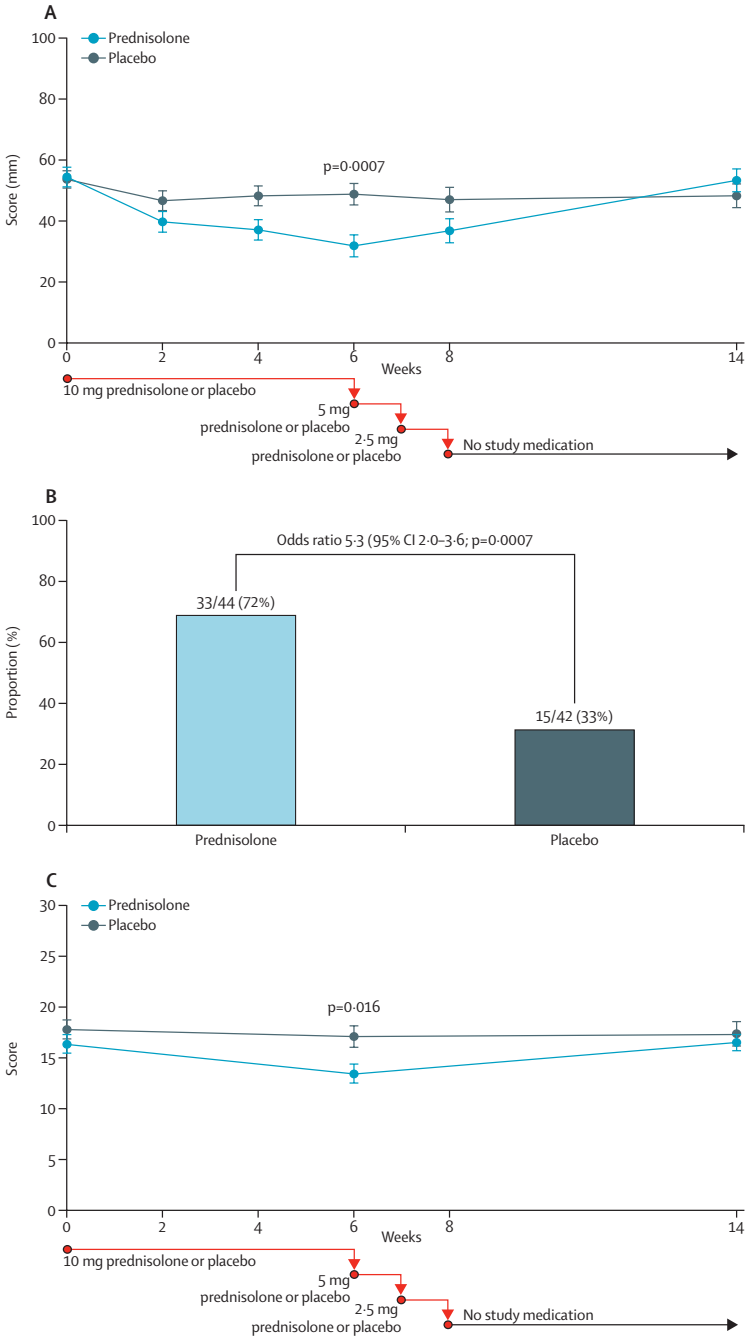

Figure 2. Visual analogue scale-reported pain in the fingers (A), the proportion of patients fulfilling Outcome Measures in Rheumatology-Osteoarthritis Research Society International responder criteria (B), and sum score of synovial thickening on ultrasound (C). Data are mean with standard error over the study period (A, C) or proportion at week 6 (B).

Table 2. Secondary clinical efficacy and imaging outcomes at week 6 (in the modified intention-to-treat population).

	Mean (SD) at baseline	
	Prednisolone (n=46)	Placebo (n=46)
Pain		
AUSCAN pain score	11.3 (3.3)	10.2 (3.1)
VAS score of pain at thumb base	34.3 (29.0)	35.4 (28.5)
Tender joint score	7.5 (6.0)	7.7 (7.3)
Function		
AUSCAN function score	18.6 (7.8)	19.0 (7.1)
FIHOA score	12.4 (5.4)	11.0 (4.7)
Short Form-36 physical component scale score*	44.6 (7.9)	46.2 (6.8)
Patient global assessment score on VAS	55.5 (21.7)	55.7 (22.0)
Soft swollen joint count	3.7 (2.7)	4.2 (2.7)
Grip strength, kg	20.4 (11.3)	20.4 (11.8)
Summed scores of imaging		
Synovial thickening (by ultrasound)	16.4 (6.3)	17.8 (6.3)
Power Doppler signal (by ultrasound)	5.3 (4.1)	7.0 (4.3)
Synovitis (by MRI)	15.6 (7.5)	14.8 (6.0)
Bone marrow lesions (by MRI)	11.0 (6.9)	11.0 (6.7)

Tender joint score was measured with the Doyle Index in the hand. AUSCAN=Australian-Canadian Hand Osteoarthritis Index. FIHOA=Functional Index for Hand Osteoarthritis. VAS=visual analogue scale. *Adjusted for baseline values and study centre. †Norm-based scores of Short Form-36 scale with a standardised mean of 50 and SD of 10 using age-specific and sex-specific Dutch population-based norms.

Mean change (SD) from baseline and week 6		Adjusted mean between-group difference (95% CI)*	p value
Prednisolone (n=46)	Placebo (n=46)		
-4.7 (3.5)	-1.1 (3.1)	-3.5 (-4.9 to -2.1)	<0.0001
-12.3 (28.0)	0.2 (17.3)	-12.0 (-21.7 to -2.3)	0.016
-3.8 (4.9)	-1.1 (8.2)	-2.7 (-5.6 to 0.1)	0.062
-6.5 (7.4)	-2.7 (4.7)	-3.7 (-6.2 to -1.1)	0.0051
-2.6 (5.1)	-0.5 (4.0)	-2.1 (-4.0 to -0.2)	0.031
3.1 (6.7)	-0.3 (6.3)	3.5 (0.8 to 6.2)	0.011
-23.6 (23.5)	-8.0 (25.3)	-15.4 (-25.6 to -5.2)	0.0031
-1.3 (2.7)	-0.9 (3.0)	-0.4 (-1.6 to 0.8)	0.53
3.5 (4.1)	2.2 (5.5)	1.2 (-0.8 to 3.2)	0.24
-2.8 (4.7)	-0.3 (5.0)	-2.5 (-4.5 to -0.5)	0.016
-1.7 (4.3)	-1.3 (4.2)	-0.4 (-2.2 to 1.4)	0.68
-0.7 (2.8)	-0.5 (2.2)	-0.2 (-1.4 to 0.9)	0.66
-0.2 (1.7)	0.5 (1.2)	-0.7 (-1.3 to -0.02)	0.043

Table 3. Reported adverse events (in the modified intention-to-treat population).

	Prednisolone (n=46)	Placebo (n=46)
Non-serious adverse events		
Total	43	43
Infections	21	25
Upper airways (including colds or coughing)	11	15
Lower airways	1	1
Urinary tract	3	1
Skin or mucosal	1	3
Gastrointestinal (including gastroenteritis)	3	4
Other	2	1
Hypertension	0	1
Hyperglycaemia*	1	3
Headache, dizziness, or lightheadedness	7	5
Hyperactivity or sleeping problems	3	0
Musculoskeletal or aspecific aches	3	3
Other†	8	6
Serious adverse events		
Total	1	4
Infected traumatic leg haematoma requiring surgery	0	1
Bowel surgery (no further information available)	0	1
Atrial fibrillation requiring pacemaker implantation	0	1
Symptomatic uterine myomas requiring hysterectomy	0	1
Myocardial infarction	1	0

One participant in the prednisolone group (who had a myocardial infarction) and three participants in the placebo group (one each with bowel surgery, Lyme disease arthritis of the knee, infected traumatic leg haematoma requiring surgery) withdrew after adverse events. *Blood glucose concentrations of at least 8.5 mmol/L (non-fasting) or at least 7.0 mmol/L (fasting) in three patients with known diabetes, and blood glucose concentrations of at least 7.8 mmol/L (non-fasting) or at least 6.5 mmol/L (fasting) in one patient with known prediabetes (metabolic syndrome). †Included stomach ache (n=3), nausea (n=1), abdominal pain after trauma (n=1), haemoptysis (no underlying pathology found in diagnostic investigations; n=1), fatigue (n=1), and urine retention (n=1) in the prednisolone group; and stomach ache (n=1), nausea (n=1), skin rash (n=1), nose bleed (n=1), peeling of skin of the hands (n=1), and postmenstrual vaginal bleeding due to uterine myomas (which required hysterectomy later during the trial, a serious adverse event; n=1) in the placebo group.

DISCUSSION

In this double-blind, randomised, placebo-controlled trial of prednisolone in patients with painful hand osteoarthritis and signs of synovial inflammation, we found that 6 weeks of treatment with 10 mg prednisolone led to a substantial reduction in finger pain. Prednisolone was consistently better than placebo in secondary outcome measures of pain and function, with a large difference in the proportion of OMERACT-OARSI responders between groups (72% *vs* 33%). MRI and ultrasound measures also showed signs of decreasing inflammation.

Previous trials of glucocorticoids in hand osteoarthritis were inconclusive. A trial[18] on the efficacy of once-daily 5 mg prednisolone for 4 weeks found that prednisolone was not superior to placebo in reducing pain. Several reasons could explain this negative result: the dosage might have been too low to reach clinical efficacy, patients had only mild disease (based on the observed radiographic damage), a substantial response to placebo lowered the ability to detect between-group differences, and half of the patients concomitantly used NSAIDs. A trial[19] of a combined prednisolone-dipyridamole preparation found that this preparation improved pain compared with placebo; however, these improvements were at the cost of more study withdrawals because of adverse events, particularly headaches, a known side-effect of dipyridamole. A trial[20] of glucocorticoid injections in DIP/PIP joints showed promising effects in the injected joint, although improvements were confined to the index joint. Moreover, by contrast with our trial, none of these studies ascertained the presence of joint inflammation through imaging at study inclusion.

By contrast with the negative results of placebo-controlled trials[9] of intra-articular glucocorticoids in patients with thumb-base osteoarthritis, we observed an improvement in thumb-base pain in the intervention group, albeit less than in the fingers. Since we deliberately excluded patients with primarily thumb-base complaints, based on evidence that thumb-base osteoarthritis is a distinct hand osteoarthritis subset that requires a distinct approach,[21] patients in our trial probably had milder radiographical damage in the thumb base, which could explain the divergent results.

Inhibitors of tumour necrosis factor and interleukin-1, two biological therapies that have been approved for the treatment of rheumatoid arthritis (the prototypical inflammatory arthritis) have not been successful in hand osteoarthritis, despite the documented role of inflammatory cytokines.[9,22] This contrasting finding suggests that, unlike in rheumatoid arthritis, targeting a single cytokine might not be sufficient in osteoarthritis.

The findings of the HOPE trial could mark a turning point in the treatment of hand osteoarthritis. The large beneficial effect size on pain and function exceeded those of all available therapeutic options in handosteoarthritis,[9] and the results showed that local inflammation in hand osteoarthritis can be modulated. The latter is an important step towards targeted treatment in hand osteoarthritis, with the eventual goal of finding a treatment that can modify its disease course.

Several clinical and imaging markers of inflammation (synovial thickening by ultrasound and bone marrow lesions by MRI) improved in the prednisolone group, yet between-group differences in other parameters did not (soft tissue swelling, PDS by ultrasound, and synovitis by

MRI). The prevalence of these outcomes might be too low, these parameters or scoring methods might not be sensitive to change or might assess several aspects of inflammation, or the 6-week treatment period might have been too short to generate large changes in these outcomes.

Although it is possible that the observed improvements in signs and symptoms in the intervention group are the result of decreased inflammation, we cannot rule out other mechanisms by which prednisolone might have led to these improvements, such as a centrally mediated effect. However, although these effects are documented for high dosages of prednisolone, there is no evidence that such effects already occur at a dosage of 10 mg per day.[23] An argument against a role of inflammation in the observed improvements could come from previous negative trials of strong anti-inflammatory drugs such as tumour necrosis factor inhibitors in hand osteoarthritis.

The clinical course of hand osteoarthritis often fluctuates, with passing flare-ups of the disease accompanied by more pain and joint inflammation. Our study findings provide evidence that such flare-ups, when patients are most in need of treatment, can be effectively and safely treated with a short course of 10 mg prednisolone. Prednisolone is an inexpensive, widely available drug, providing ample opportunity to directly apply these findings in daily clinical practice. However, although the HOPE trial established the efficacy of prednisolone in patients with pain and joint inflammation, of whom most reported a flare-up after withdrawal of pain medication, no data are available on whether other patients with hand osteoarthritis would benefit from this drug, although it is likely that joint inflammation is a prerequisite for its effectiveness. This hypothesis is also supported by findings from an open study,[24] showing that synovial thickening on ultrasound was the most important predictor for response to 120 mg intramuscular methylprednisolone in patients with inflammatory hand pain.

After tapering the study medication, symptoms resumed baseline levels, analogously to discontinuation of anti-inflammatory therapies in other rheumatic musculoskeletal diseases. Although the observed symptomatic effect at week 6 was substantial, it is unknown whether further improvement would have been achieved with continued treatment. It also remains to be seen whether timely suppression of inflammation can eventually alter the disease course. Future studies to investigate the optimal dosage and duration of treatment are warranted, possibly in trials employing treat-to-target strategies.

We found no safety signals for a short course of 10 mg prednisolone daily, but prolonged glucocorticoid treatment can lead to serious complications, the risk of which increases with increased dose and duration of therapy. A particularly relevant complication is the development of osteoporosis, since a large proportion of patients with hand osteoarthritis are (postmenopausal) women aged 50 years or older. Bone loss and increased vertebral and non-vertebral fracture risk can occur rapidly after initiation of glucocorticoid therapy.[25,26] A systematic literature review[27] found a dose-dependent increased risk of bone mineral density loss, osteoporosis, and vertebral and non-vertebral fractures with chronic, daily use of 7.5-30 mg of a prednisolone equivalent. Although the mean daily dose in these studies was comparable to that in the HOPE trial, their treatment duration and cumulative dose were substantially higher (1840-30240 mg *vs* 472.5 mg in the HOPE trial). Nevertheless, since our trial only provides evidence for the effectiveness of a 6-week course of 10 mg prednisolone daily, and in light of the risk of complications such as

glucocorticoid-induced osteoporosis, prescription of prednisolone for prolonged periods of time in patients with hand osteoarthritis should be discouraged. Notably, NSAIDs, which are widely used for symptom relief in patients with painful hand osteoarthritis, are also often unsuitable or, indeed, contraindicated, even for a short period of time, because of their established high risks of cardiac, gastrointestinal, and renal adverse events and because of drug-drug interactions with many other drugs, such as antihypertensive medication.[28-30]

Inclusion of a specific subset of patients (ie, with signs of active inflammation), is both a strength and a limitation of our study. Although it reduces the generalisability of the results to patients without this characteristic, it increased the likelihood of observing an effect of a targeted intervention. The heterogeneous nature of the disease necessitates clear patient stratification in clinical trials to identify patients who will most likely benefit from treatment. Liberal patient inclusion might have been a reason that previous trials in hand osteoarthritis produced negative results.

In conclusion, 6-week treatment with 10 mg prednisolone effectively improved signs and symptoms compared with placebo in patients with painful hand osteoarthritis and signs of synovial inflammation. The results of our study provide clinicians with a new short-term treatment option for patients with hand osteoarthritis who report a flare-up of their disease.

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