Intra-articular botulinum toxin A injection for painful base-of-thumb osteoarthritis: a double-blind, randomised, controlled, phase 3 trial (RHIBOT)

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See **Comment** page e453

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Summary

Background Intra-articular botulinum toxin A injection might have analgesic effects in patients with joint diseases. We aimed to compare the effects of intra-articular botulinum toxin A injection with those of intra-articular saline injection for patients with painful base-of-thumb osteoarthritis.

Methods RHIBOT was a double-blind, randomised, controlled, phase 3 trial conducted at Cochin Hospital, Paris, France. We recruited adult patients with x-ray evidence of trapeziometacarpal osteoarthritis who fulfilled the 1990 American College of Rheumatology criteria for hand osteoarthritis and reported a pain intensity score of at least 30 on an 11-point numeric rating scale (0: no pain to 100: maximal pain). Participants were randomly assigned (1:1), using a computer-generated randomisation list with permuted blocks of variable size (4 or 6), to receive an ultrasound-guided injection of either botulinum toxin A (50 Allergan units) in 1 mL of saline (experimental group) or 1 mL of saline alone (control group) in the trapeziometacarpal joint, in addition to custom-made rigid splinting. The primary outcome was the mean change from baseline in base-of-thumb pain in the previous 48 h on a numeric rating scale at 3 months after injection, analysed by intention to treat. This study is registered with ClinicalTrials.gov, NCT03187626.

Findings Between Nov 2, 2018, and Nov 3, 2020, we assessed 370 individuals for eligibility and recruited 60 (16%) participants (mean age 64·9 years [SD 9·4], 47 [78%] women and 13 [22%] men), of whom 30 (50%) participants were randomly assigned to the experimental group and 30 (50%) to the control group. At baseline, base-of-thumb pain score was 60·0 of 100·0 (SD 15·9). At 3 months, the mean reduction in base-of-thumb pain was –25·7 (95% CI –35·5 to –15·8) in the experimental group and –9·7 (–17·1 to –2·2) in the control group (absolute difference –16·0 [–28·1 to –3·9]; p=0·043). Overall, 51 adverse events were reported in both groups: 27 (53%) in the experimental group and 24 (47%) in the control group. During follow-up, 14 (47%) participants in the experimental group and two (7%) participants in the control group reported mild transient motor deficit of the thenar muscle. No serious adverse events were reported.

Interpretation Botulinum toxin A could be considered as a fast-acting, intra-articular therapy targeting chronic pain in individuals with base-of-thumb osteoarthritis. Future studies are needed to investigate the potential mechanism of the effects observed in this trial, to replicate our findings, and to assess the effects of repeated injections over time and their clinical effectiveness, including an analysis of cost-effectiveness.

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Introduction

The base of the thumb is a frequent location of osteoarthritis.[1] Trapeziometacarpal osteoarthritis (also known as base-of-thumb osteoarthritis) affects middle-aged (aged 50–65 years) and older (aged ≥65 years) individuals and results in base-of-thumb pain and limitations in hand-specific activities.[1] For the medium and long term, evidence suggests that splinting could reduce pain and improve hand function.[2,3] In 2009, in a multicentre, randomised, controlled trial of 112 participants (101 [90%] women) with base-of-thumb osteoarthritis, our group showed that a custom-made night-time splint (n=57) reduced pain and improved hand function at 1 year compared with usual care (n=55).[2] For the short term, a combination of conservative treatments is recommended,[4] with small-to-moderate treatment effect.[5] However, use of intra-articular treatments (eg, glucocorticoids and hyaluronan) for the short and medium term is currently debated.

Systematic reviews have found conflicting evidence regarding the effect of intra-articular glucocorticoid or hyaluronan injection on base-of-thumb pain.[6–9] In 2018, the European Alliance of Associations for Rheumatology

Research in context

Evidence before this study

The effectiveness of intra-articular treatments for painful base-of-thumb osteoarthritis is debated. We searched PubMed from date of database inception to Sept 27, 2021, using the search terms "intra-articular" AND "base-of-thumb"AND "osteoarthritis" for publications in English and French. Systematic reviews reported conflicting evidence regarding the effect of intra-articular glucocorticoid or hyaluronan injections on base-of-thumb pain. In 2018, the European Alliance of Associations for Rheumatology recommended that intra-articular glucocorticoid injection should not generally be used in patients with hand osteoarthritis. In the 2019 American College of Rheumatology guidelines for managing hand osteoarthritis, intra-articular glucocorticoid injection was conditionally recommended for patients with hand osteoarthritis and intra-articular hyaluronan injection was conditionally not recommended in patients with base-of-thumb osteoarthritis.

Added value of this study

In this double-blind, randomised, controlled, phase 3 trial, we found that intra-articular botulinum toxin A injection with custom-made rigid splinting in patients with painful base-of-thumb osteoarthritis reduced base-of-thumb pain at 1 month and 3 months after intervention, compared with intra-articular saline injection with splinting.

Implications of all the available evidence

Botulinum toxin A could be considered as a fast-acting, intra-articular therapy targeting chronic pain in individuals with base-of-thumb osteoarthritis. Future studies are needed to explore the effects of repeated injections over time.

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recommended that intra-articular glucocorticoid injection should not generally be used in patients with hand osteoarthritis, but remains equivocal about its use in the interphalangeal joint due to scarcity of evidence.[4] In the 2019 American College of Rheumatology (ACR) guidelines for managing hand osteoarthritis, intra-articular glucocorticoid injection was conditionally recommended for patients with hand osteoarthritis and intra-articular hyaluronan injection was conditionally not recommended in patients with base-of-thumb osteoarthritis.[10]

Use of intra-articular botulinum toxin A injection as a pain modulator in joint diseases has raised interest over the past decade. Botulinum toxin A is a neurotoxin produced by *Clostridium botulinum* that inhibits acetylcholine release into the synaptic cleft in cholinergic nerve terminals. The clinical effects of botulinum toxin A injection for spasticity have been shown to last for up to 3 months following administration.[11] Additionally, treatment with botulinum toxin A showed intrinsic antinociceptive effects in various animal models (ie, murine, equine, and canine) of joint diseases.[12] In a trial of 176 participants with knee osteoarthritis, McAlindon and colleagues[13] compared the effects of intra-articular botulinum toxin A injection with those of intra-articular saline injection on knee pain, finding no reduction in pain at 8 weeks. However, subgroup analyses of this study suggested positive effects of botulinum toxin A injection for up to 3 months in participants with nociceptive pain.[14] One trial of base-of-thumb osteoarthritis was publicly registered on Jan 11, 2010, but was terminated early because the researchers were unable to acquire the additional funding needed to continue the study, and no data were analysed (NCT01045694).

In the current trial, we aimed to compare the effects of intra-articular botulinum toxin A injection with those of intra-articular saline injection in patients with painful base-of-thumb osteoarthritis. We hypothesised that intra-articular botulinum toxin A injection, as an add-on therapy to custom-made rigid splinting, could reduce base-of-thumb pain at 3 months.

Methods

Study design

RHIBOT was a double-blind, randomised, controlled, phase 3 trial conducted at Cochin Hospital, Paris, France. Participants were recruited among inpatients and outpatients of the physical and rehabilitation medicine department of this tertiary care centre. We started recruitment on Nov 2, 2018, and follow-up was completed on April 23, 2021. This trial is reported in accordance with the CONSORT statement (appendix pp 14–16).[15,16] No changes in inclusion criteria or outcomes occurred after trial commencement. The protocol of the study was approved by the Comité de Protection des Personnes Tours Ouest-1 (région Centre) on Dec 19, 2017 (number IORG0008143 OMB: 0990–0279) and was published on June 30, 2018.[17] The original and final versions of our protocol and statistical analysis plan are available in the appendix (pp 17–143). All amendments to the original protocol were approved by our institutional review board and are reported in the appendix (p 2). Written informed consent was obtained from all participants.

See Online for appendix

Participants

The participant inclusion criteria were assessed by three board-certified specialists (CN, CD, and GC) in physical and rehabilitation medicine with experience as trialists. Patients were eligible for inclusion if they were aged at least 18 years; reported a pain intensity score of at least 30 on a self-administered 11-point pain numeric rating scale (0: no pain to 100: maximal pain); reported pain involving the base of the thumb; showed x-ray evidence of

trapeziometacarpal osteoarthritis with at least two of the following items involving the trapeziometacarpal joint: osteophytes, joint space narrowing, subchondral bone sclerosis, or subchondral cysts; and fulfilled the 1990 ACR classification criteria for hand osteoarthritis adapted to trapeziometacarpal osteoarthritis.[18] Participant exclusion criteria were history of thumb surgery, inflammatory or crystal-associated rheumatic disease, or epilepsy; neurological disorders involving the hands other than carpal tunnel syndrome; collagen disorders involving the hands (eg, Dupuytren's contracture, Marfan syndrome, or Ehlers-Danlos syndrome); osteoarthritis predominating at the scaphotrapezial joint on x-ray; bilateral trapeziometacarpal osteoarthritis without a predominant painful side; hand or wrist trauma or intra-articular treatments for up to 2 months; contraindication to botulinum toxin A injection or to splinting; assessment impossible because of cognitive or behavioural disorders; pregnancy and breastfeeding; inability to speak, read, or write French; and individuals referred to in articles L 1121–5, L 1121–6, L 1121–8, or L 1121–9 of the French public health code (which refer to protected children or adults, or individuals under guardianship or trusteeship). Individuals excluded for temporary reasons could be rescreened.

Randomisation and masking

Participants were randomly assigned (1:1) to receive either intra-articular botulinum toxin A injection with splinting (experimental group) or intra-articular saline injection with splinting (control group). An independent statistician (LJ) from the Unité de Recherche Clinique–Centre d'Investigation Clinique Paris Descartes Necker–Cochin (Hôpital Tarnier, Paris, France) provided a computer-generated randomisation list with permuted blocks of variable size (4 or 6). Randomisation involved use of a secured software (CleanWeb, Telemedicine Technologies SAS, Boulogne-Billancourt, France). Participants, investigators, occupational therapists, radiologists, statisticians, and treating physicians were masked to the allocation group. The pharmacist who prepared the solution to inject was not masked, but had no contact with participants, investigators, statisticians, or health-care personnel. Prepared solutions for both the experimental group and control group had the same volume (1 mL), colour, viscosity, and echogenicity.

Procedures

On the same day as randomisation and baseline assessment, participants allocated to the experimental group received a single ultrasound-guided injection of 50 Allergan units of onabotulinum toxin A (Botox, Allergan, Irvine, CA, USA) in 1 mL of saline in the trapeziometacarpal joint of one hand, as described previously.[17] This target joint was selected on the basis of the patient reporting pain at the base of the thumb, consistent clinical examination (ie, on the same side as pain), and x-ray findings of trapeziometacarpal osteoarthritis. The target side was the hand reported by the patient to be the most painful. The dose regimen and the choice of onabotulinum toxin A were decided on the basis of findings from a small unpublished trial (NCT01045694). Briefly, two board-certified radiologists (HG and RC) performed all of the injections in a masked and standardised manner. Ultrasonography scoring for synovitis and osteophytes was performed in a standardised manner with a prespecified checklist, as described previously.[19] The intra-articular injection was performed through the thenar muscles while the patient was supine with the hand lying palm up on the table. Botulinum toxin A was injected in the trapeziometacarpal joint using a 25 g needle measuring 25 mm long under ultrasound control and aseptic conditions. Correct positioning was assessed by visualising the tip of the needle in the joint recess and by tracing air and solution in the joint.[20] No subcutaneous or intra-articular anaesthetic was injected.

Participants allocated to the control group received a single ultrasound-guided injection of 1 mL of saline in the trapeziometacarpal joint, following the same procedure as the experimental group. No subcutaneous or intra-articular anaesthetic was injected. We chose saline to act as the control treatment because there was no evidence to suggest that other intra-articular treatments or non-injection-based comparators[7,8] were superior to saline and because saline volume, colour, viscosity, and echogenicity were similar to those of botulinum toxin A.

On the same day as the intra-articular injection, participants in both groups received a thermoformable plastic rigid splint, which had been custom-made by four experienced occupational therapists (CB, FC, ER, and RF), as described previously.[2,17] Participants were instructed to wear the splint continuously for 48 h after the injection and then during each night for 6 months, as the standard of care. No specific measures to enhance adherence to splinting were implemented. To ensure consistent delivery of custom splints, all four therapists were part of the same team, and three of them participated in designing the protocol and the intervention (CB, FC, and ER). Non-pharmacological and pharmacological cointerventions were allowed to be prescribed as needed in both groups by the treating physician and were reported by the participant using a standardised checklist to be recorded in the electronic case report form at 1, 3, and 6 months. No guidance was given to treating physicians and participants to control use of other analgesics.

Immediately after injection and at 6 months, the credibility of interventions and the expectations of participants were assessed by the credibility and expectancy questionnaire.[21]

Outcomes

We selected our primary and secondary efficacy outcomes in accordance with the 2015 Osteoarthritis

Research Society International recommendations,[22] which took into account guidelines from the regulatory agencies (ie, US Food and Drug Administration[23] and European Medicines Agency[24]), and with the 2017 guidelines for the conduct of pharmacological clinical trials in hand osteoarthritis of the European Society on Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases.[25] The primary efficacy outcome was mean change from baseline in base-of-thumb pain on the painful side (either left or right) in the 48 h previous to the interview on a self-administered 11-point numeric rating scale at 3 months after injection, analysed by intention to treat (ie, in all randomly assigned participants in the groups to which they were allocated). The 3-month timepoint was recommended by the European Society on Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases for fast-acting drugs.[25] The investigator checked that the participants' self-reported pain intensity corresponded to the side injected during face-to-face follow-up visits.

Secondary efficacy outcomes were mean change from baseline in base-of-thumb pain in the previous 48 h on a self-administered 11-point numeric rating scale at 1 month and 6 months after injection; mean change from baseline in hand-specific activity limitations in the previous 2 weeks on the self-administered Cochin Hand Function Scale (0: no limitations to 90: maximal limitations)[26] at 3 months and 6 months; mean change from baseline in patient global assessment on a self-administered 11-point numeric rating scale (0: worst possible condition to 100: best possible condition) at 3 months and 6 months; the Osteoarthritis Research Society International–Outcome Measures in Rheumatology[27] response at 3 months and 6 months; and the self-reported consumption of analgesics and non-steroidal anti-inflammatory drugs on a self-administered four-category scale (ie, never, several times a month, several times a week, or daily) at 3 months and 6 months. To minimise the data collectors' influence on participants' answers, participants were instructed to complete self-administered questionnaires from home at 3 months and 6 months, before the scheduled follow-up visit.

Safety outcomes were assessed by the investigator by asking an open-ended question (ie, "Have you had any adverse events since last contact?") at 3 months and 6 months. The investigator assessed the causality relationship between the adverse event and the administered treatment using the WHO–Uppsala Monitoring Centre method.

Statistical analysis

With an α risk of 0·05, a power (1-β) of 0·80, and a predicted difference in mean change from baseline of 15 points (SD 20) on the base-of-thumb pain numeric rating scale at 3 months favouring the experimental group (corresponding to an effect size of 0·75 [95% CI 0·21 to 1·28]), we needed 29 patients in each group. 15 points on the pain numeric rating scale is considered to be the minimal clinically meaningful difference in pain for patients with hand osteoarthritis.[28] The SD used for the power calculation was based on data published previously.[28] Estimating that 3·3% of participants would be lost to follow-up, we sought to include 30 participants in each group.

Quantitative variables are described with mean (SD) or mean (95% CI), and categorical variables with frequencies and percentages. To estimate the differences in mean change from baseline between groups for quantitative outcomes, we used a constrained longitudinal data analysis, in which the baseline value was included in the response vector together with the post-baseline values, and a constraint of a common baseline mean across treatment groups was imposed on the model. For missing data on the primary and secondary efficacy outcomes at 1, 3, and

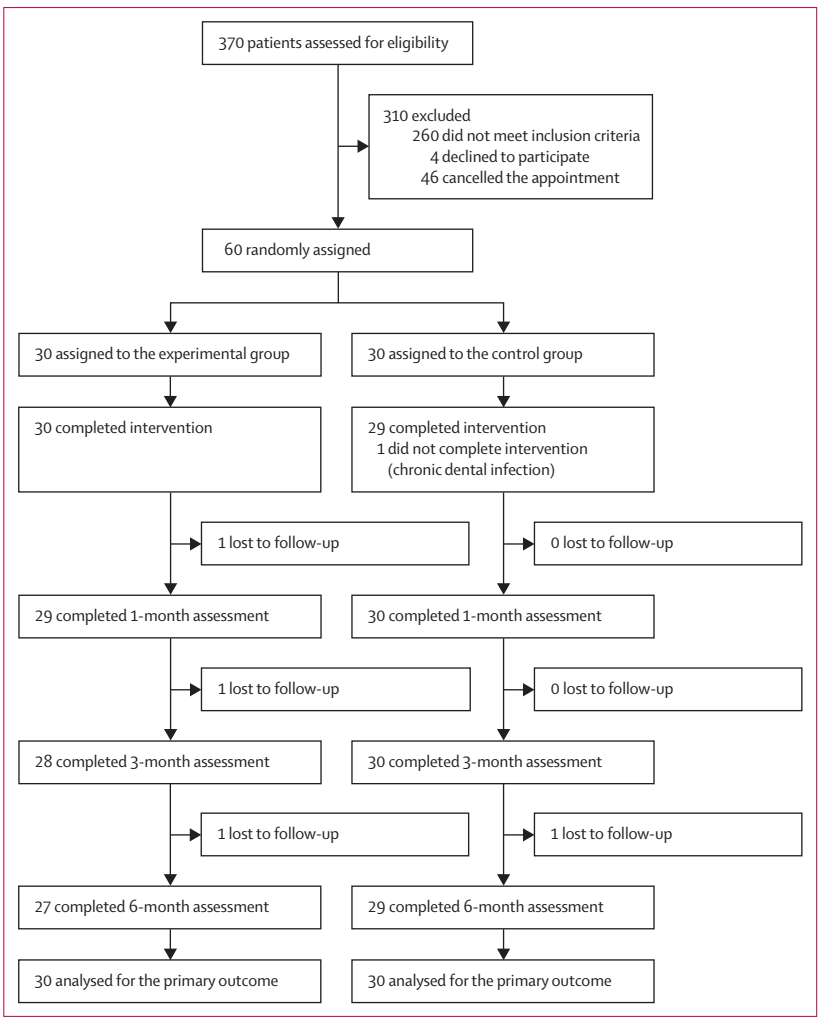

Figure 1: **Trial profile**

	Experimental group (n=30)	Control group (n=30)	Total (n=60)
Age, years	65·2 (8·2)	64·6 (10·4)	64·9 (9·4)
Sex			
Female	25 (83%)	22 (73%)	47 (78%)
Male	5 (17%)	8 (27%)	13 (22%)
Body mass index, kg/m²	26·1 (5·4)	24·8 (4·4)	25·4 (4·9)
Missing data	1 (3%)	0 (0)	1 (2%)
Higher education	25 (83%)	24 (80%)	49 (82%)
Missing data	0 (0)	0 (0)	0 (0)
Employment status			
Full-time or part-time employment	14 (47%)	13 (43%)	27 (45%)
Unemployment	1 (3%)	0 (0)	1 (2%)
Unable to work	0 (0)	2 (7%)	2 (3%)
Sick leave	0 (0)	1 (3%)	1 (2%)
Retired	15 (50%)	14 (47%)	29 (48%)
Missing data	0 (0)	0 (0)	0 (0)
Family history of trapeziometacarpal osteoarthritis	17 (59%)	12 (40%)	29 (49%)
Missing data	1 (3%)	0 (0)	1 (2%)
Previous intra-articular treatments			
Intra-articular hyaluronan injection	2 (7%)	2 (7%)	4 (7%)
Missing data	2 (7%)	0 (0)	2 (3%)
Intra-articular glucocorticoid injection	8 (27%)	7 (23%)	15 (25%)
Missing data	0 (0)	0 (0)	0 (0)
Current treatments			
Oral analgesics	9 (31%)	6 (22%)	15 (27%)
Missing data	1 (3%)	3 (10%)	4 (7%)
Oral NSAIDs	4 (15%)	2 (7%)	6 (11%)
Missing data	3 (10%)	3 (10%)	6 (10%)
Topical NSAIDs	6 (21%)	11 (37%)	17 (29%)
Missing data	2 (7%)	0 (0)	2 (3%)
Symptomatic slow-acting drugs for osteoarthritis	2 (7%)	0 (0)	2 (4%)
Missing data	3 (10%)	3 (10%)	6 (10%)
Base-of-thumb splint*	11 (42%)	16 (59%)	27 (51%)
Missing data	4 (13%)	3 (10%)	7 (12%)
Home-based exercises†	3 (12%)	9 (32%)	12 (22%)
Missing data	4 (13%)	2 (7%)	6 (10%)
Physiotherapy	3 (11%)	5 (18%)	8 (15%)
Missing data	3 (10%)	2 (7%)	5 (8%)
Clinical characteristics			
Right-handed	26 (87%)	27 (90%)	53 (88%)
Missing data	0 (0)	0 (0)	0 (0)
Dominant side injected	14 (47%)	17 (57%)	31 (52%)
Missing data	0 (0)	0 (0)	0 (0)
Manual activity level in the past 3 months (NRS 0–100)‡	64·8 (27·2)	50·0 (28·2)	57·4 (28·5)
Missing data	1 (3%)	1 (3%)	2 (3%)
Base-of-thumb pain intensity in the previous 48 h (NRS 0–100)§	61·7 (13·4)	58·3 (18·2)	60·0 (15·9)
Missing data	0 (0)	0 (0)	0 (0)
Base-of-thumb pain duration, months	74·5 (80·3)	53·9 (53·5)	64·0 (68·2)
Missing data	1 (3%)	0 (0)	1 (2%)
Cochin Hand Function Scale score (0–90)¶	31·7 (16·8)	28·5 (18·8)	30·1 (17·7)
Missing data	0 (0)	0 (0)	0 (0)
Patient global assessment (NRS 0–100)‖	72·0 (18·8)	71·7 (17·8)	71·8 (18·2)
Missing data	0 (0)	0 (0)	0 (0)
Right thumb opposition (Kapandji index 0–10)	9·2 (1·3)	9·2 (0·9)	9·2 (1·1)
Missing data	0 (0)	0 (0)	0 (0)
Right thumb counter-opposition (Kapandji index 1–4)	2·8 (0·9)	2·8 (1·0)	2·8 (1·0)
Missing data	0 (0)	0 (0)	0 (0)
Left thumb opposition (Kapandji index 0–10)	9·1 (1·6)	9·0 (1·2)	9·0 (1·4)
Missing data	0 (0)	0 (0)	0 (0)
Left thumb counter-opposition (Kapandji index 1–4)	3·0 (0·9)	2·7 (1·1)	2·9 (1·0)
Missing data	0 (0)	0 (0)	0 (0)
Ultrasound findings			
Synovitis			
Grade 0	2 (7%)	5 (17%)	7 (12%)
Grade 1	17 (57%)	13 (45%)	30 (51%)
Grade 2	7 (23%)	5 (17%)	12 (20%)
Grade 3	4 (13%)	6 (21%)	10 (17%)
Missing data	0 (0)	1 (3%)	1 (2%)
Osteophytes			
Grade 1	2 (7%)	3 (10%)	5 (9%)
Grade 2	12 (40%)	17 (59%)	29 (49%)
Grade 3	16 (53%)	9 (31%)	25 (42%)
Missing data	0 (0)	1 (3%)	1 (2%)

Data are mean (SD) or n (%). NRS=numeric rating scale. NSAIDs=non-steroidal anti-inflammatory drugs. *If participants already had a custom-made rigid splint, the splint was revised by occupational therapists and participants were instructed to wear it as prespecified in the protocol. †Including base-of-thumb mobility and strengthening exercises. ‡Higher scores indicate greater manual activity level. §Higher scores indicate greater pain. ¶Higher scores indicate more limitations. ‖Higher scores indicate better health.

Table 1: **Baseline demographic and clinical characteristics**

6 months, we used imputation carried forward from baseline observation. In patients receiving botulinum toxin A, a post-hoc Student's *t* test was performed to compare the mean change in pain intensity from baseline between patients with and without thenar muscle motor

	Experimental group (n=30)	Control group (n=30)	Absolute difference (95% CI)	Relative risk (95% CI)	p value
Primary efficacy outcome					
3 months after injection					
Change in base-of-thumb pain score (NRS 0–100)*	−25·7 (−35·5 to −15·8)	−9·7 (−17·1 to −2·2)	−16·0 (−28·1 to −3·9)	NA	0·043
Secondary efficacy outcomes					
1 month after injection					
Change in base-of-thumb pain score (NRS 0–100)*	−34·3 (−42·9 to −25·7)	−18·0 (−26·2 to −9·8)	−16·3 (−27·9 to −4·7)	NA	0·0039
3 months after injection					
Change in Cochin Hand Function Scale score (0–90)†	−7·3 (−12·3 to −2·3)	−5·8 (−11·2 to −0·3)	−1·5 (−8·8 to 5·7)	NA	0·85
Change in PGA (NRS 0–100)‡	0·3 (−5·7 to 6·4)	−3·7 (−9·0 to 1·7)	4·0 (−3·9 to 11·4)	NA	0·25
OARSI–OMERACT response	22 (73%)	18 (60%)	13·3 (−10·3 to 37·0)	1·2 (0·9 to 1·8)	0·27
Missing data	0 (0)	0 (0)	0 (0)	..	..
Analgesics since last contact	12 (43%)	8 (28%)	15·3 (−9·2 to 39·8)	1·6 (0·8 to 3·2)	0·23
Missing data	2 (7%)	1 (3%)	3 (5%)	..	..
NSAIDs since last contact	5 (18%)	4 (14%)	3·6 (−15·6 to 22·8)	1·3 (0·4 to 4·2)	0·71
Missing data	2 (7%)	2 (7%)	4 (7%)	..	..
6 months after injection					
Change in base-of-thumb pain score (NRS 0–100)*	−18·3 (−26·9 to −9·8)	−11·7 (−21·2 to −2·2)	−6·7 (−19·2 to 5·9)	NA	0·37
Change in Cochin Hand Function Scale score (0–90)†	−7·5 (−13·5 to −1·5)	−4·6 (−10·8 to 1·6)	−2·9 (−11·3 to 5·5)	NA	0·66
Change in PGA (NRS 0–100)‡	−6·7 (−13·0 to −0·4)	−5·7 (−11·6 to 0·3)	−1·0 (−9·5 to 7·5)	NA	0·82
OARSI–OMERACT response	17 (57%)	20 (67%)	−10·0 (−34·5 to 14·5)	0·9 (0·6 to 1·3)	0·43
Missing data	0 (0)	0 (0)	0 (0)	..	..
Use of analgesics since last contact	14 (52%)	11 (39%)	12·6 (−13·6 to 38·7)	1·3 (0·7 to 2·4)	0·35
Missing data	3 (10%)	2 (7%)	5 (8%)	..	..
Use of NSAIDs since last contact	6 (25%)	6 (21%)	3·6 (−19·5 to 26·6)	1·2 (0·4 to 3·1)	0·76
Missing data	6 (20%)	2 (7%)	8 (13%)	..	..

Data are mean (95% CI) or n (%). NRS=numeric rating scale. NA=not applicable. PGA=patient global assessment. OARSI=Osteoarthritis Research Society International. OMERACT=Outcome Measures in Rheumatology. NSAIDs=non-steroidal anti-inflammatory drugs. *Higher scores indicate greater pain. †Higher scores indicate more limitations. ‡Higher scores indicate better health.

Table 2: **Primary and secondary efficacy outcomes**

deficit. These results are expressed as differences in mean change from baseline with 95% CI at 3, 6, and 12 months. To estimate differences in categorical outcomes between the groups, we used χ^2 or Fisher's exact test, as appropriate. Results are expressed as absolute risk differences and relative risks with corresponding 95% CIs.

All statistical analyses were done using SAS (version 9.4). No interim analysis was performed and no adjustment for multiplicity was made. All tests were two-tailed with an α risk of 5%. This study is registered with ClinicalTrials.gov, NCT03187626.

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 Nov 2, 2018, and Nov 3, 2020, we assessed 370 individuals for eligibility and from Nov 19, 2018, we recruited 60 (16%) participants, of whom 30 (50%) participants were randomly assigned to the experimental group and 30 (50%) to the control group. Overall, 59 (98%) of 60 participants completed the allocated intervention (figure 1). Mean age of participants was 64·9 years (SD 9·4), 47 (78%) were female and 13 (22%) were male (table 1). At baseline, the mean base-of-thumb pain score was 60·0 of 100·0 (SD 15·9) and mean duration of symptoms was 64·0 months (68·2). Among the 59 participants with ultrasound assessments at baseline, synovitis grade was up to 1 of 3 for 37 (63%) participants and osteophyte grade was at least 2 of 3 in 54 participants (92%; table 1). For all 59 participants who received the allocated intervention, randomisation, baseline assessment, and interventions were performed on the same day. Demographic and clinical characteristics disaggregated by sex are provided in the appendix (pp 3–6).

At 3 months after injection, the mean reduction in base-of-thumb pain was significantly greater in the experimental group than in the control group (−25·7 [95% CI −35·5 to −15·8] *vs* −9·7 [−17·1 to −2·2]; absolute difference −16·0 [−28·1 to −3·9]; p=0·043; table 2; figure 2; appendix pp 7–10). At 1 month after injection, the mean reduction in base-of-thumb pain was significantly greater in the experimental group than in the control group (standardised mean difference −0·72

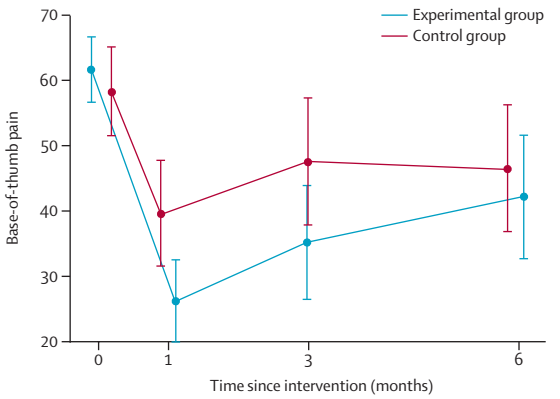

Figure 2: **Mean base-of-thumb pain intensity in the previous 48 h, by intervention group**
Data are mean (95% CI).

[–1·24 to –0·19]), with no difference at 6 months (table 2). At 3 months after injection, the Osteoarthritis Research Society International–Outcome Measures in Rheumatology response was 73% (22 of 30 participants) in the experimental group and 60% (18 of 30 participants) in the control group (table 2). Secondary outcomes did not differ between the experimental group and control group (table 2; appendix pp 7–10).

During follow-up, 51 adverse events were reported in both groups: 27 in the experimental group and 24 in the control group (table 3). No serious adverse events were reported. During injection, two (3%) of 60 participants, both in the control group, reported an adverse event (one localised bleeding and one increased base-of-thumb pain). During follow-up, 14 (47%) participants in the experimental group and two (7%) participants in the control group reported mild transient (≤8 weeks) motor deficit of the thenar muscle (table 3). Base-of-thumb pain reduction at 3 months was of the same magnitude in participants who had a motor deficit and in those who did not (–30·8 [95% CI –46·5 to –15·2] *vs* –22·2 [–35·9 to –8·5]; p=0·39).

The radiologist considered the positioning of the needle tip to be correct in all 59 participants who had received the intervention. During injection, mean base-of-thumb pain score was 70·3 of 100·0 (SD 21·2) and mean score for acceptability of the procedure was 74·6 of 100·0 (30·4). Immediately after injection, participants rated the predicted success of the injection in reducing symptoms; the mean score for which was 8·0 of 9·0 (SD 1·5) in the experimental group and 7·4 of 9·0 (2·2) in the control group (appendix p 11). At 6 months, we observed no imbalance in the credibility of interventions between groups (appendix p 11). At 1, 3, and 6 months, we observed no imbalance in non-pharmacological and pharmacological cointerventions between the experimental group and the control group (appendix pp 12–13).

	Experimental group (n=30)	Control group (n=30)	Total (n=60)
Serious adverse events	0 (0)	0 (0)	0 (0)
Adverse events	27 (90%)	24 (80%)	51 (85%)
Base-of-thumb pain	6 (20%)	11 (37%)	17 (28%)
Thenar muscle motor deficit	14 (47%)	2 (7%)	16 (27%)
Other musculoskeletal pain	5 (17%)	6 (20%)	11 (18%)
Intercurrent infection	1 (3%)	2 (7%)	3 (5%)
Thumb paraesthesia	1 (3%)	1 (3%)	2 (3%)
Localised bleeding	0 (0)	1 (3%)	1 (2%)
Thrombophlebitis	0 (0)	1 (3%)	1 (2%)

Data are n (%).

Table 3: **Safety outcomes**

Discussion

In this randomised controlled trial of intra-articular botulinum toxin A injection with splinting for patients with painful base-of-thumb osteoarthritis, the mean reduction in base-of-thumb pain was significantly greater in the experimental group than in the control group 1 month and 3 months after the intervention. We found no imbalance in cointerventions or credibility of treatments. The magnitude and time of response in the control group was consistent with previous reports of the placebo effect in osteoarthritis.[29]

In this trial, pain intensity at baseline was high but the synovitis grade was low in most participants, which suggested a limited contribution of local inflammation. In two randomised controlled trials of base-of-thumb osteoarthritis, treating local inflammation with either fluoroscopically guided intra-articular glucocorticoid injection (n=40 participants)[30] or landmark-guided intra-articular glucocorticoid injection (n=60 participants)[31] did not reduce base-of-thumb pain in the short term (12 weeks) or medium term (24 weeks). Compared with the effects of oral glucocorticoid use for hand osteoarthritis, we did not observe an early pain flare-up.[32] The mechanisms of chronic pain in osteoarthritis vary by both location and time interval. Because botulinum toxin A can reduce not only the release of mediators involved in nociceptor sensitisation (eg, substance P, calcitonin gene-related peptide, glutamate, and nerve growth factor) but also the secretion of neurotransmitters involved in peripheral and central sensitisation, botulinum toxin A might target more than one pathway contributing to chronic pain.

In this trial, 14 (47%) of 30 participants in the experimental group reported a mild transient motor deficit of the thenar muscle. This off-target effect might have contributed to pain reduction. However, base-of-thumb pain reduction at 3 months was of the same magnitude in participants who had a motor deficit and in those who did not.

As per standard of care, participants were provided with a custom-made rigid splint in addition to

intra-articular treatments.[2,3,33] It is possible that rigid splinting might have synergistically enhanced the effects of intra-articular botulinum toxin A injection, or that some potentiation of off-loading of botulinum toxin A and splint together occurred. However, in our previous study,[2] which investigated custom-made rigid splinting (n=55) versus usual care (n=46), the standardised mean difference between groups was only –0·01 (95% CI –0·40 to 0·38) for pain reduction at 1 month, compared with –0·72 (–1·24 to –0·19) in this trial.

Our results differed from the observations of McAlindon and colleagues[13] in a trial of participants with knee osteoarthritis. The authors found no reduction in knee pain at any time during the 24-week follow-up between participants who received intra-articular injection of botulinum toxin A and those who received saline.[13] Several reasons could explain the differences between the findings of both studies. The diagnosis of chronic knee pain can include conditions other than osteoarthritis, whereas the diagnosis of base-of-thumb pain related to osteoarthritis is more specific. Furthermore, with respect to joint volume, the dose used in the current trial for the trapeziometacarpal joint (50 Allergan units per mL, considering that the trapeziometacarpal joint volume is 1 mL) was 12·5-fold to 25·0-fold higher than that used by McAlindon and colleagues[13] (2–4 Allergan units per mL, considering that the knee joint volume is 100 mL).

We found no positive effects of intra-articular botulinum toxin A injection on pain at 6 months and in other secondary outcomes at 3 months and 6 months, and Osteoarthritis Research Society International–Outcome Measures in Rheumatology responder rates were no different, suggesting no improvement on function or patient global assessment in the experimental group. These results were not surprising because the biological effects of botulinum toxin A only last for up to 3 months,[11] and because our study was not primarily designed to assess these outcomes.[17] Overall, our interventions were acceptable. We found no serious adverse events. Mild transient motor deficit of the thenar muscle was frequent in the experimental group but was expected. This adverse event might be prevented by injecting a smaller volume or dose of botulinum toxin A, or both.

A limitation of this trial is that we recruited participants from a single centre and that our sample size was small, which could be associated with larger treatment effect estimates. Ethnicity data were not collected as part of this trial so any differential effects of this treatment by race or ethnicity could not be estimated. We did not record the use of any other device, and no guidance was given to physicians and participants to control use of other analgesics. Therefore, it is possible that both recorded and non-recorded cointerventions might have affected outcomes. Additionally, we did not collect data on the new initiation of therapy, which could have influenced outcomes. However, allowing cointerventions in both groups aimed to reflect the standard of care used in real-world settings. The dose regimen and choice of botulinum toxin A were based on a small unpublished trial (NCT01045694). Assessment of other botulinum toxin A formulations and a dose-optimisation schedule could be considered in future research. We did not ask participants if they thought that they had received the active drug or the placebo, and we did not include a blinding index or question as part of the design, which might have affected the estimated treatment effect. Notably, almost half of participants in the experimental group reported a mild transient motor deficit of the thenar muscle and this could have reasonably contributed to unmasking in the experimental group. Therefore, it is possible that the treatment effects were overestimated. We did not consider recording the involvement of the interphalangeal joint. It is unknown whether asking participants to rate pain in the base of the thumb could have been influenced by how painful fingers in the same hand were. Furthermore, hand strength is considered to be a core domain in trials of hand osteoarthritis but was not measured in this trial, and the distribution of participants with comorbid carpal tunnel syndrome between the intervention groups was not recorded. Like tanezumab, botulinum toxin A targets action of nerve growth factor. Because safety concerns have been raised with tanezumab regarding bone necrosis, long-term trials are needed to fully explore the safety of intra-articular botulinum toxin A injection. Finally, generalisability of our findings may be limited: recruitment was done at one site over a period of time, mean age of participants was relatively old (64·9 years [SD 9·4]), 310 (84%) of 370 individuals assessed for eligibility were excluded, and the use of custom splinting might have affected the ability to generalise the effects of the injection.

In summary, the absolute mean change from baseline in base-of-thumb pain intensity at 1 month and 3 months after injection was greater in participants who received an intra-articular injection of 50 Allergan units of botulinum toxin A than in those who received an intra-articular injection of saline. Botulinum toxin A could be considered as a fast-acting, intra-articular therapy targeting chronic pain in individuals with base-of-thumb osteoarthritis. Future studies are needed to investigate the potential mechanism of the effects observed in this trial, to replicate our findings, and to assess the effects of repeated injections over time and their clinical effectiveness, including an analysis of cost-effectiveness.

Contributors

CN, HA, SP, and FR conceptualised and designed the study. CN, HA, RC, HG, CGi, SP, and FR drafted the original protocol. CN obtained the funding. CN coordinated the study. CN, RC, HG, CB, FC, GC, CD, RF, M-ML-C, and AR acquired the data. CN, HA, and LJ designed the statistical analysis plan. CN, HA, and LJ verified the data. HA and LJ accessed the raw data. CN, HA, LJ, and FR analysed and interpreted the data. CN drafted the original manuscript. HA, LJ, and FR reviewed and

provided comments on the manuscript. All authors approved the final version. CN and FR take responsibility for the integrity of the work as a whole, from inception to finished Article. CN and FR had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

CN reports receiving consulting fees from Thuasne; speaker fees from Actelion Pharmaceuticals France, Ipsen, and Meda Pharmaceuticals; reimbursement of conference registration and accommodation by Grünenthal and Merz; and hospitality from Preciphar, Takeda France, UCB Pharma SA, and Sandoz, outside of the submitted work. CD reports receiving hospitality from Merz, outside of the submitted work. All other authors declare no competing interests.

Data sharing

The full original protocol and dataset can be accessed by academic researchers by contacting CN (christelle.nguyen2@aphp.fr) and statistical codes can be accessed by contacting LJ (lea.jilet@aphp.fr). Data collected for the study, including individual participant data and a data dictionary defining each field in the set, will be made available to others. Deidentified participant data and data dictionary will be made available. The study protocol and statistical analysis plan are available in the appendix (pp 17–143). Data will be shared without investigator support, after approval of a proposal, with a signed data access agreement, for research purposes.

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References

1 Poole JU, Pellegrini VD Jr. Arthritis of the thumb basal joint complex. *J Hand Ther* 2000; **13:** 91–107.
2 Rannou F, Dimet J, Boutron I, et al. Splint for base-of-thumb osteoarthritis: a randomized trial. *Ann Intern Med* 2009; **150:** 661–69.
3 Spaans AJ, van Minnen LP, Kon M, Schuurman AH, Schreuders AR, Vermeulen GM. Conservative treatment of thumb base osteoarthritis: a systematic review. *J Hand Surg Am* 2015; **40:** 16–21.
4 Kloppenburg M, Kroon FP, Blanco FJ, et al. 2018 update of the EULAR recommendations for the management of hand osteoarthritis. *Ann Rheum Dis* 2019; **78:** 16–24.
5 Deveza LA, Robbins SR, Duong V, et al. Efficacy of a combination of conservative therapies vs an education comparator on clinical outcomes in thumb base osteoarthritis: a randomized clinical trial. *JAMA Intern Med* 2021; **181:** 429–38.
6 Trellu S, Dadoun S, Berenbaum F, Fautrel B, Gossec L. Intra-articular injections in thumb osteoarthritis: a systematic review and meta-analysis of randomized controlled trials. *Joint Bone Spine* 2015; **82:** 315–19.
7 Kroon FPB, Carmona L, Schoones JW, Kloppenburg M. Efficacy and safety of non-pharmacological, pharmacological and surgical treatment for hand osteoarthritis: a systematic literature review informing the 2018 update of the EULAR recommendations for the management of hand osteoarthritis. *RMD Open* 2018; **4:** e000734.
8 Riley N, Vella-Baldacchino M, Thurley N, Hopewell S, Carr AJ, Dean BJF. Injection therapy for base of thumb osteoarthritis: a systematic review and meta-analysis. *BMJ Open* 2019; **9:** e027507.
9 Hamasaki T, Laprise S, Harris PG, et al. Efficacy of nonsurgical interventions for trapeziometacarpal (thumb base) osteoarthritis: a systematic review. *Arthritis Care Res (Hoboken)* 2020; **72:** 1719–35.
10 Kolasinski SL, Neogi T, Hochberg MC, et al. 2019 American College of Rheumatology/Arthritis Foundation Guideline for the management of osteoarthritis of the hand, hip, and knee. *Arthritis Rheumatol* 2020; **72:** 220–33.
11 Brashear A, Gordon MF, Elovic E, et al. Intramuscular injection of botulinum toxin for the treatment of wrist and finger spasticity after a stroke. *N Engl J Med* 2002; **347:** 395–400.
12 Nguyen C, Lefèvre-Colau MM, Poiraudeau S, Rannou F. Evidence and recommendations for use of intra-articular injections for knee osteoarthritis. *Ann Phys Rehabil Med* 2016; **59:** 184–89.
13 McAlindon TE, Schmidt U, Bugarin D, et al. Efficacy and safety of single-dose onabotulinumtoxinA in the treatment of symptoms of osteoarthritis of the knee: results of a placebo-controlled, double-blind study. *Osteoarthritis Cartilage* 2018; **26:** 1291–99.
14 Arendt-Nielsen L, Jiang GL, DeGryse R, Turkel CC. Intra-articular onabotulinumtoxinA in osteoarthritis knee pain: effect on human mechanistic pain biomarkers and clinical pain. *Scand J Rheumatol* 2017; **46:** 303–16.
15 Schulz KF, Altman DG, Moher D, Group C. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *BMJ* 2010; **340:** c332.
16 Boutron I, Altman DG, Moher D, Schulz KF, Ravaud P, Group CN. CONSORT statement for randomized trials of nonpharmacologic treatments: a 2017 update and a CONSORT extension for nonpharmacologic trial abstracts. *Ann Intern Med* 2017; **167:** 40–47.
17 Gil C, Abdoul H, Campagna R, et al. Intra-articular botulinum toxin A for base-of-thumb osteoarthritis: protocol for a randomised trial (RHIBOT). *BMJ Open* 2018; **8:** e022337.
18 Altman R, Alarcón G, Appelrouth D, et al. The American College of Rheumatology criteria for the classification and reporting of osteoarthritis of the hand. *Arthritis Rheum* 1990; **33:** 1601–10.
19 Keen HI, Lavie F, Wakefield RJ, et al. The development of a preliminary ultrasonographic scoring system for features of hand osteoarthritis. *Ann Rheum Dis* 2008; **67:** 651–55.
20 Qvistgaard E, Kristoffersen H, Terslev L, Danneskiold-Samsøe B, Torp-Pedersen S, Bliddal H. Guidance by ultrasound of intra-articular injections in the knee and hip joints. *Osteoarthritis Cartilage* 2001; **9:** 512–17.
21 Borkovec T, Nau S. Credibility of analogue therapy rationales. *J Behav Ther Exp Psychiatry* 1972; **3:** 257–60.
22 Kloppenburg M, Maheu E, Kraus VB, et al. OARSI clinical trials recommendations: design and conduct of clinical trials for hand osteoarthritis. *Osteoarthritis Cartilage* 2015; **23:** 772–86.
23 US Food and Drug Administration. Osteoarthritis: structural endpoints for the development of drugs. August, 2018. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071577.pdf (accessed Sept 27, 2021).
24 European Medicines Agency. Committee for medicinal products for human use (CHMP): guideline on clinical investigation of medicinal products used in the treatment of osteoarthritis. http://www.ema.europa.eu/ema/pages/includes/document/open_document.jsp?webContentId=WC500003440 (accessed Sept 27, 2021).
25 Reginster JL, Arden NK, Haugen IK, et al. Guidelines for the conduct of pharmacological clinical trials in hand osteoarthritis: consensus of a working group of the European Society on Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO). *Semin Arthritis Rheum* 2018; **48:** 1–8.
26 Duruöz MT, Poiraudeau S, Fermanian J, et al. Development and validation of a rheumatoid hand functional disability scale that assesses functional handicap. *J Rheumatol* 1996; **23:** 1167–72.
27 Pham T, van der Heijde D, Altman RD, et al. OMERACT-OARSI initiative: osteoarthritis Research Society International set of responder criteria for osteoarthritis clinical trials revisited. *Osteoarthritis Cartilage* 2004; **12:** 389–99.
28 Tubach F, Ravaud P, Martin-Mola E, et al. Minimum clinically important improvement and patient acceptable symptom state in pain and function in rheumatoid arthritis, ankylosing spondylitis, chronic back pain, hand osteoarthritis, and hip and knee osteoarthritis: results from a prospective multinational study. *Arthritis Care Res (Hoboken)* 2012; **64:** 1699–707.
29 Zhang W, Robertson J, Jones AC, Dieppe PA, Doherty M. The placebo effect and its determinants in osteoarthritis: meta-analysis of randomised controlled trials. *Ann Rheum Dis* 2008; **67:** 1716–23.

30 Heyworth BE, Lee JH, Kim PD, Lipton CB, Strauch RJ, Rosenwasser MP. Hylan versus corticosteroid versus placebo for treatment of basal joint arthritis: a prospective, randomized, double-blinded clinical trial. *J Hand Surg Am* 2008; **33:** 40–48.

31 Meenagh GK, Patton J, Kynes C, Wright GD. A randomised controlled trial of intra-articular corticosteroid injection of the carpometacarpal joint of the thumb in osteoarthritis. *Ann Rheum Dis* 2004; **63:** 1260–63.

32 Kroon FPB, Kortekaas MC, Boonen A, et al. Results of a 6-week treatment with 10 mg prednisolone in patients with hand osteoarthritis (HOPE): a double-blind, randomised, placebo-controlled trial. *Lancet* 2019; **394:** 1993–2001.

33 Bertozzi L, Valdes K, Vanti C, Negrini S, Pillastrini P, Villafañe JH. Investigation of the effect of conservative interventions in thumb carpometacarpal osteoarthritis: systematic review and meta-analysis. *Disabil Rehabil* 2015; **37:** 2025–43.