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Original article

Genicular artery embolization for knee osteoarthritis: Results of the LipioJoint-1 trial

Marc Sapoval[1,2,*], Charles Querub[1], Helena Pereira[3,4], Olivier Pellerin[1,2], Tom Boeken[1,5], Alessandro Di Gaeta[1], Marc Al Ahmar[1], Marie-Martine Lefevre-Colau[6,7], Christelle Nguyen[6,8], Camille Daste[6,7], Maxime Lacroix[9], Jean-Denis Laredo[10], Brigitte Sabatier[5,11,12], Nicolas Martelli[11,13], Gilles Chatellier[3,4], Carole Déan[1], François Rannou[6,8]

[1] *Assistance Publique-Hôpitaux de Paris, Hôpital Européen Georges Pompidou, Department of Vascular and Oncological Interventional Radiology, 75015 Paris, France*
[2] *Université Paris Cité, PARCC - INSERM Unité-970, 75015 Paris, France*
[3] *INSERM, Centre d'investigation Clinique 1418 Épidémiologie Clinique, 75015 Paris, France*
[4] *Assistance Publique-Hôpitaux de Paris, Hôpital Européen Georges-Pompidou, Clinical Research Unit, 75015 Paris, France*
[5] *HeKA team, INRIA, 75012 Paris, France*
[6] *Assistance Publique-Hôpitaux de Paris, Hôpital Cochin, Service de Rééducation et de Réadaptation de l'Appareil Locomoteur et des Pathologies du Rachis, 75014 Paris, France*
[7] *Université de Paris Cité, INSERM UMR-S 1153, Centre de Recherche Épidémiologie Et Statistique Paris (CRESS), ECaMO Team, 75004 Paris, France*
[8] *Université Paris Cité, INSERM UMR-S 1124, Toxicité Environnementale, Cibles Thérapeutiques, Signalisation Cellulaire et Biomarqueurs (T3S), Campus Saint-Germain-des-Prés, 75006 Paris, France*
[9] *Assistance Publique-Hôpitaux de Paris, Hôpital Européen Georges-Pompidou, Service d'imagerie, 75015 Paris, France*
[10] *Assistance Publique-Hôpitaux de Paris, Hôpital Lariboisière, Service de Chirurgie Orthopédique Et Traumatologique, 75010 Paris, France*
[11] *Assistance Publique-Hôpitaux de Paris, Hôpital Européen Georges-Pompidou, Pharmacie, 75015 Paris, France*
[12] *Université Paris-Saclay, Faculté de Pharmacie, Pharmacie Clinique, 91400 Orsay, France*
[13] *Université Paris-Saclay, Faculté de Pharmacie, GRADES, 91400 Orsay, France*

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ABSTRACT

Purpose: The purpose of this study was to evaluate the safety and efficacy of transient genicular artery embolization (GAE) using an ethiodized oil-based emulsion for the treatment of knee osteoarthritis (KOA).
Materials and methods: This prospective, single-arm, open-label, multicenter, first-in-human cohort trial was registered on ClinicalTrials.gov (NCT04733092). The main inclusion criterion was diagnosis of KOA according to a visual analogue scale (VAS) pain score ≥ 40 mm (score range: 0–100 mm), despite conservative treatment for at least three months. Treatment efficacy was assessed using changes in VAS pain score, Mean Western Ontario & McMaster Universities osteoarthritis (WOMAC) function score (normalized to 100; score ranging from 0 to100) and outcome measures in rheumatoid arthritis clinical trials (OMERACT)-Osteoarthritis Research Society (OARSI) set of responder criteria.
Results: Twenty-two consecutive participants (13 women; mean age, 66 ± 9 [standard deviation (SD)]) were included and underwent GAE. Emulsion consisted in a mixture of ioversol and ethiodized oil (ratio 1:3, respectively) prepared extemporaneously. The rate of serious adverse events attributed to GAE within one month was 5% (1/22), corresponding to reversible worsening of renal function. Immediate technical success rate was 100%. Mean VAS pain score dropped from 74.4 ± 16.5 (SD) mm at baseline to 37.2 ± 26.7 (SD) mm at three months ($P < 0.001$). Mean WOMAC function score (normalized to 100: score ranging from 0 to 100) decreased from 57.3 ± 17.1 (SD) at baseline to 33.5 ± 25.9 (SD) at three months ($P < 0.001$). At three months, 16 out of 22 participants (73%) were considered responders according to the OMERACT-OARSI set of responder criteria, including high improvement in either pain or WOMAC function, or improvement in both pain and WOMAC function.
Conclusion: GAE using an ethiodized oil-based emulsion is safe and improves pain and function in participants with KOA for at least three months.

Abbreviations: GAE, Genicular arteries embolization; KL, Kellgren-Lawrence; KOA, Knee osteoarthritis; OARSI, Osteoarthritis Research Society; OMERACT, Outcome measures in rheumatoid arthritis clinical trials; SD, Standard deviation; VAS, Visual analogic scale; WOMAC, Western Ontario and McMaster Universities osteoarthritis index

* Corresponding author.
E-mail address: marc.sapoval2@aphp.fr (M. Sapoval).

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1. Introduction

Osteoarthritis is a very common progressive musculoskeletal disease with an estimated prevalence of 13.4% in Europe [1]. Osteoarthritis can affect all joints, but predominantly weight-bearing joints such as the hip and knee [2–4]. Knee osteoarthritis (KOA) generates 2% of years lived with disability, and patients often have to reduce their work and leisure activities [5,6]. There is no cure for KOA, and current therapeutic strategies are used to reduce disease progression and to mitigate symptoms [7]. Nonsteroidal anti-inflammatory drugs are the medications of choice, associated with non-pharmacological treatments, followed by intra-articular glucocorticoid or hyaluronic acid injection. Neurotomy or neuromodulation techniques can also be considered [8]. Ultimately, total or partial knee replacement is offered for patients with persistent and severe pain [9]. There is a need for minimally invasive techniques allowing for conservative management in patients in whom surgery is not indicated [10].

Angiogenesis and inflammatory mediators are known to play a role in the development of KOA [11]. Inflammation drives synovial angiogenesis, and proangiogenic factors are known to stimulate nerve growth [12]. Neovascularization and the accompanying sensory neonerves have been hypothesized to be one of the sources of pain in osteoarthritis. Moreover, knee inflammation probably drives peripheral and central sensitization which is associated with pain severity [13]. Targeting angiogenesis and inflammation could thus contribute to reduce pain severity in KOA.

Based on these assumptions, Okuno et al. proposed genicular artery embolization (GAE) using imipenem/cilastatin to treat symptomatic KOA with good results on pain relief [14]. However, this antibiotic is not available worldwide in this indication, thus limiting this approach. Since then, studies have demonstrated that GAE is effective in reducing pain and disability without major complications using permanent microparticles [15–18]. However, permanent embolization of genicular arteries carries a risk of ischemic skin and/or bone damage [19]. Assuming the optimal embolic agent for GAE would be a temporary one and available worldwide, it was hypothesized that GAE using an ethiodized oil-based emulsion, whose temporary embolizing properties and safety for use in human are well-known, would be safe and effective [20–22].

The purpose of this prospective, single-arm, first-in-human clinical trial was to evaluate the safety and efficacy of temporary GAE using an ethiodized oil-based emulsion for the treatment of painful KOA.

2. Materials and methods

2.1. Study design

LipioJoint-1 was a prospective, single-arm, open-label, first-in-human cohort trial performed in two academic centers having received approval from the relevant ethics committee. All participants provided written informed consent. The study was funded by a grant from Guerbet and was sponsored by Assistance Publique-Hôpitaux de Paris (AP-HP; Délégation à la Recherche Clinique et à l'Innovation, Paris, France). It was conducted under the guidance of an independent data and safety monitoring board convened by AP-HP. This study was registered on ClinicalTrials.gov (NCT04733092).

All consecutive patients of two academic hospitals (recruiting medical centers) between March 2021 and June 2022 were assessed for eligibility. Main inclusion criteria were primary KOA according to the American College of Rheumatology classification and of Kellgren-Lawrence (KL) grade ≥ 2; visual analogue scale (VAS) pain score ≥ 40 mm despite analgesic medication for at least three months; failure or intolerance of or patient unwilling to take opioid treatment; failure or refusal of intra-articular corticosteroid injection; patient not eligible for surgery (or refusing surgery) [23–25].

Main exclusion criteria were intra-articular injection in target joint within the previous three months; treated hyperthyroidism; traumatic injury, current hemarthrosis or bleeding in the target joint within the last week; known severe allergy to iodinated agents; stage 3 or higher chronic kidney disease (creatinine clearance < 60 mL/min); patient unable or unwilling to comply with the follow-up schedule; participation in another interventional study.

2.2. Ethiodized oil-based emulsion preparation

Emulsion consisted in a mix of 1:3 (v:v) ioversol 300 mgI/ml (Optiray® 300, Guerbet) and ethiodized oil (Lipiodol® Ultra-Fluide, Guerbet) prepared extemporaneously in the angiography room. Using a dedicated mixing and injection system (Vectorio®, Guerbet), 2 mL of ioversol were gently pushed into 6 mL of ethiodized oil followed by 20 back-and-forth movements to obtain a homogeneous emulsion.

2.3. Genicular artery embolization

All GAEs were performed under local anesthesia by a panel of two interventional radiologists (CQ and MS) with five and twenty years of experience in arterial embolization, respectively. All GAEs were performed through antegrade ipsilateral femoral artery puncture. A Cobra C 2.5-Fr diagnostic catheter (Cordis) and a 1.7-Fr Pursue microcatheter (Merit Medical, Inc) were typically used for selective angiogram and super-selective embolization of the target arteries. The microcatheter was gently pushed as distally as possible into the artery feeding the hypervascular typical blush of KOA. All the arteries supplying painful areas were super-selectively embolized. The emulsion was injected slowly into the arteries and appeared as multiple, radiopaque deformable droplets slowly conveyed by the arterial flow. The endpoint was total arterial occlusion. Control angiogram of the foot was performed at the end of embolization to excluded potential migration of embolic material.

2.4. Outcomes

Follow-up consisted in a clinical evaluation by a trial investigator (interventional radiologist or rheumatologist) at one week, one month and three months. Adverse events were collected at each visit to assess safety. Efficacy was assessed using validated patient questionnaires, the VAS pain and Western Ontario and McMaster Universities osteoarthritis index (WOMAC) questionnaire (Likert scale normalized to 100; score ranging from 0 to 100 mm) and evaluated at each visit [26]. All adverse events were reviewed by the independent data and safety monitoring medical board (JPB, FB, EC, CLB).

The primary outcome was the rate of serious adverse events attributed to GAE within one month. Secondary outcomes included immediate technical success rate (success of catheterization and embolization of at least one target artery), number of adverse events, rate of responders (outcome measures in rheumatoid arthritis clinical trials - Osteoarthritis Research Society (OMERACT-OARSI) set of responder criteria), rate of participants reaching the patient acceptable symptom state defined as a VAS score of < 32.3 mm, and questionnaire scores at follow-up [27,28]. OMERACT-OARSI set of responder criteria were defined as either significant improvement in pain or in WOMAC function (relative change ≤ −50% and absolute change ≤ −20) or improvement in both pain and WOMAC function (relative change ≤ −20% and absolute change ≤ −10). Severity of adverse events was assessed using the classification of the Society for Interventional Radiology [29].

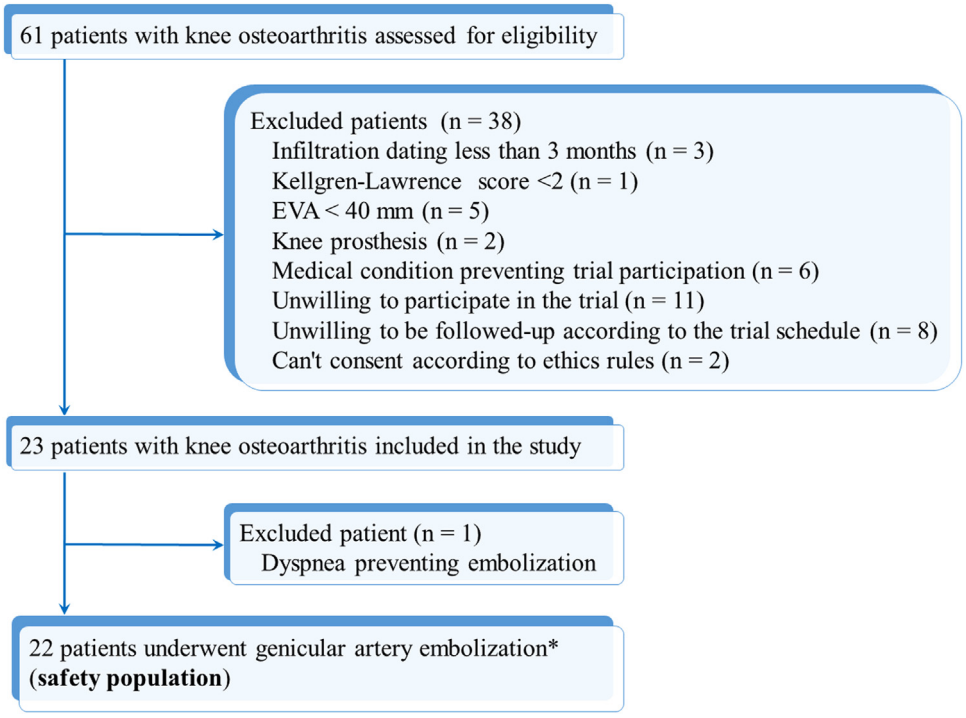

Fig. 1. Study flowchart. *One patient was included twice for the embolization of his second knee (the second inclusion was performed five months after the first one).

2.5. Statistical analysis

All analyses are reported according to the STROBE statement (http://www.strobe-statement.org/). The main analysis was conducted on an intention-to-treat basis. Since this trial was a first-in-human trial with a safety primary endpoint, sample size and power were not calculated. Sample size was chosen based on the estimated enrolment rate and acceptable study length. The normality of the distribution of continuous variables was assessed using Shapiro-Wilk test [30]. Continuous variables were expressed as means ± standard deviations (SD) for normally distributed data and otherwise as medians and ranges. Categorical data were expressed as raw numbers, proportions and percentages. Missing data were not replaced. Paired *t*-tests or Wilcoxon matched-pairs signed-rank tests were used for within-group comparisons between each follow-up visit and baseline.

Analyses were performed with the SAS software, version 9.4 (SAS Institute). A P value < 0.05 was considered to indicate significant difference.

3. Results

3.1. Participants' characteristics

Among 61 patients assessed for eligibility, 22 consecutive participants were included in the trial (Fig. 1). There were 13/22 (59%) women and 9/22 (41%) men, with a mean age of 66 ± 9 (SD) years. One of these participants took part in the trial on two consecutive occasions and underwent embolization of both knees in two separate sessions (five months apart). Twenty-two out of 22 (100 %) participants completed the three months' follow-up. All participants had moderate to severe KOA, with KL grade 3 and 4 for 10/22 (46%) and 12/22 (54%) participants, respectively. At inclusion, mean VAS pain score was 74.4 ± 16.5 (SD) mm despite level 1 or level 2 analgesic medication for 22/22 (100%) and 10/22 (45%) participants respectively. Mean WOMAC function and index scores were 57.3 ± 17.1 (SD) (range: 16–62) and 58.4 ± 15.7 (SD) (range: 27–85) respectively. Eleven out of 22 (50%) participants had bilateral osteoarthritis and 15 (68%) described morning stiffness in the target knee. Eighteen out of 22 (82%) participants had received intra-articular corticosteroid injections in the target knee more than three months before inclusion (Table 1). Among the 9/22 (41%) participants requiring analgesic medication the week before GAE, 2/22 (9%) required level 2 analgesia.

3.2. GAE procedure details

A median of two (range: 1–4) arteries per knee were embolized with 0.9 ± 0.3 (SD) mL of emulsion per artery (Fig. 2). Data on the procedure are provided in Table 2.

Table 1
Characteristics of the 22 participants.

Variables	Values
Age (year)	66 ± 9 [48–79]
Women	13 (13/22; 59%)
BMI (kg/m^2)	31.0 ± 5.3 [22.4–47.4]
Target knee (right)	14 (14/22; 64%)
Kellgren and Lawrence score	
3	10 (10/22; 45%)
4	12 (12/22; 55%)
VAS pain score (0–100 mm)	74.4 ± 16.5 [50.0–100.0]
WOMAC* (0–100 mm)	
Index	58.4 ± 15.7 [28.1–88.5]
Pain	59.3 ± 13.7 [40.0–85.0]
Stiffness	65.3 ± 18.5 [37.5–100.0]
Function	57.3 ± 17.1 [23.5–91.2]
Pathological compartment (most painful)	
Medial	14 (14/22; 64%)
Lateral	6 (6/22; 27%)
Femoropatellar	2 (2/22; 9%)

Continuous variables are expressed as means ± standard deviations. Categorical data are expressed as raw numbers, followed by proportions and percentages into parentheses. BMI: body mass index, VAS: Visual analog scale, WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index.

* WOMAC scores were normalized to 100 (score range 0–100 mm).

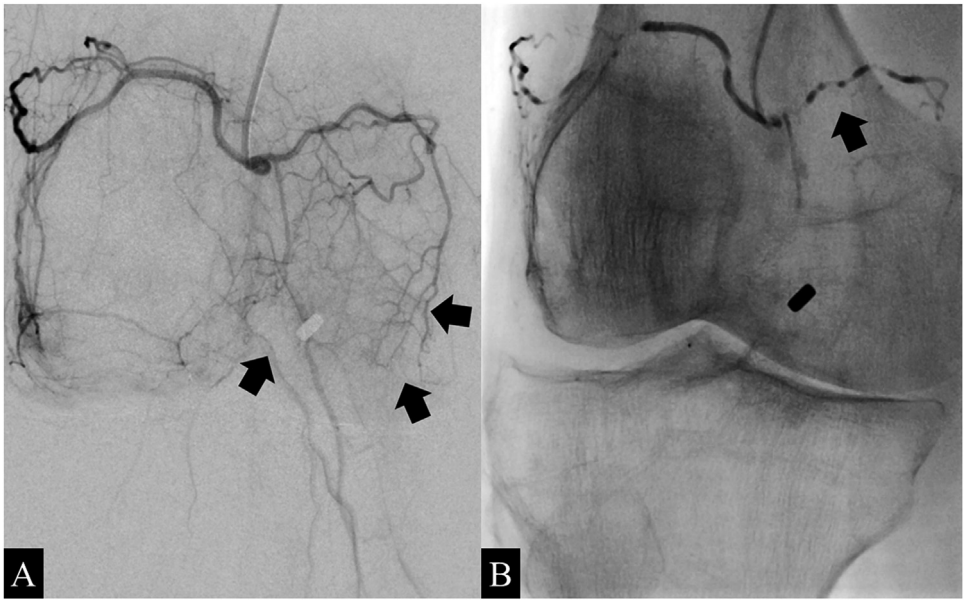

Fig. 2. Angiograms of the right knee in a 76-year-old man with Kellgren and Lawrence grade 3 knee osteoarthritis.
A, Before embolization, selective angiography of the common trunk of superior lateral and superior medial genicular arteries shows hypervascular inflammatory blush (arrows).
B, During embolization using ethiodized oil of the common trunk, angiogram shows emulsion droplets (arrows).

The immediate technical success rate was 100% (22/22). No patient described pain during GAE. No adverse events occurred during GAE. Control angiograms did not reveal any occlusion of the distal arterial network.

The first five participants were hospitalized overnight in observation in order to monitor local outcome. Thereafter, GAE was performed on an outpatient basis and participants were instructed to contact the interventional radiology department in the event of pain or any local symptoms (at the puncture site or on the target knee).

3.3. GAE safety analysis

The rate of serious adverse events attributed to GAE within one month was 5% (1/22), corresponding to a clinically significant increase in serum creatinine beginning one day after GAE (baseline, 82 μmol/L; maximal level at day 2, 156 μmol/L), which then returned to normal 13 days later (classified as serious adverse event) in a 79-year-old woman. No worsening of knee pain was reported immediately after GAE. One participant experienced knee edema for four days, associated with erythema lasting two days after embolization (classified as mild adverse event). Another participant experienced erythema of the target knee for four hours (classified as mild adverse event). No skin ulceration, local paraesthesia or puncture site complications were observed.

Table 2
Genicular artery embolization procedural data in 22 participants.

Variables	Values
Hypervascular arteries	
Descending genicular artery	16 (16/22; 73%)
Superior medial genicular artery	10 (10/22; 45%)
Superior lateral genicular artery	8 (8/22; 36%)
Inferior medial genicular artery	13 (13/22; 59%)
Inferior lateral genicular artery	6 (6/22; 27%)
Recurrent genicular artery	2 (2/22; 9%)
Fluoroscopy time (min)	15.5 ± 5.4 [7.7–28.3]
Radiation dose (mGray)	75.6 ± 33.1 [16.0–126.0]
Dose area product (μGray/m^2)	1350.5 (1080.0, 2495.0)

Continuous variables are expressed as means ± standard deviations (SD) for normally distributed variables and medians (Q1, Q3) otherwise. Categorical data are expressed as raw numbers followed by proportions and percentages into parentheses.

3.4. Clinical efficacy of GAE

Knee pain and function improved from one week to three months after GAE (Table 3, Fig. 3). Mean VAS pain score decreased from 74.4 ± 16.5 (SD) mm (range: 50–100 mm) at baseline to 37.2 ± 26.7 (SD) mm (range: 0–100 mm) at three months ($P < 0.001$). WOMAC function score (normalized to 100; score ranging from 0 to 100) at three months decreased to 33.5 ± 25.9 (SD) (range: 0–67), representing a mean change from baseline of −23.6 ± 22.7 (SD) ($P < 0.001$). At one and three months, 16/21 (76%) and 16/22 (73%) participants were considered responders according to the OMERACT-OARSI set of responder criteria respectively [27].

Among 10 participants with KL grade 3, 8 (80%) were considered responders at three months. Among 12 participants with KL grade 4, eight (67%) were considered responders at three months. At three months, 9/22 (41%) participants reached a patient acceptable symptom state (VAS pain score < 33.2 mm) (Table 4) [28].

4. Discussion

This is the first report on the use of ethiodized oil in a musculoskeletal indication. The results of our study demonstrate that transient GAE, using an ethiodized oil-based emulsion, is safe and effective in the treatment of symptomatic KOA. The only procedure-related complication was a reversible deterioration in renal function, likely related to the injection of an iodinated contrast agent for intra-arterial navigation.

Previous experiences with other embolic material have demonstrated a good overall safety profile but not without possible side effects [16,18]. The safest embolic agent seems to be imipenem/cilastatin, but it is not accessible in several countries. In their systematic review, Torkian et al. reported that a total of 54/214 participants (25.2%) experienced minor adverse events, most commonly, self-resolving transient skin ischemia [31]. In another systematic review, Casadaban et al. reported transient erythema of the skin in the region of GAE without ulceration in a total of 21 out of 186 (11%)

Table 3
Pain and Western Ontario and McMaster Universities osteoarthritis index scores change after genicular artery embolization.

	1 week				1 month				3 months			
Variable	n	1 week	Change	*P* value	n	1 month	Change	*P* value	n	3 months	Change	*P* value
VAS pain score (0–100 mm)	22	35.5 ± 22.9	−38.9 ± 26.3	<0.001	21	37.2 ± 21.3	−36.0 ± 20.6	<0.001	22	37.2 ± 26.7	−37.2 ± 28.2	<0.001
WOMAC (0–100 mm)												
Pain	22	32.6 ± 21.6	−26.4 ± 20.1	<0.001	21	36.0 ± 21.3	−22.9 ± 21.4	<0.001	22	35.9 ± 26.4	−23.4 ± 23.7	<0.001
Stiffness	22	36.4 ± 22.8	−29.0 ± 23.9	<0.001	21	41.7 ± 24.2	−23.8 ± 25.0	<0.001	22	40.9 ± 30.9	−24.4 ± 29.5	<0.001
Function	21	30.8 ± 24.2	−26.2 ± 23.1	<0.001	20	33.5 ± 23.7	−23.3 ± 23.1	<0.001	21	33.5 ± 25.9	−23.6 ± 22.7	<0.001
Index	20	32.8 ± 23.1	−25.1 ± 21.2	<0.001	20	34.6 ± 22.5	−23.2 ± 22.1	<0.001	21	34.7 ± 25.9	−23.5 ± 22.6	<0.001

Variables are expressed as means ± standard deviations.
VAS indicates visual analog scale, WOMAC indicates Western Ontario and McMaster Universities osteoarthritis index.
WOMAC scores are normalized to 100 (score range 0–100 mm).
* Change: Mean change from baseline.

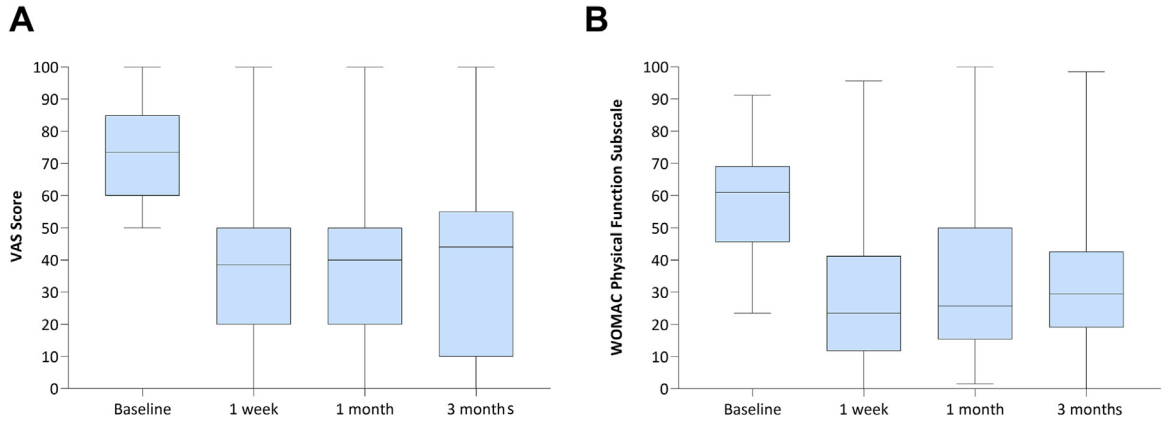

Fig. 3. Change in visual analog scale (VAS) pain score (A) and Western Ontario and McMaster Universities osteoarthritis index (WOMAC) function score (B) over the three-month follow-up period.
Symptoms are improved when scores decrease. WOMAC function score is normalized to 100 (score ranging from 0 to100 mm).

participants, which resolved without intervention in all patients. The events occurred in 17/27 (63%) of GAEs using permanent microparticles, lasting one to three months, and in 4/159 (2.5%) of GAEs using imipenem/cilastatin lasting about three weeks [19]. In order to reduce this risk of non-target embolization and subsequent skin, nerve and/or bone ischemia, researchers have suggested the application of ice pads to create vasoconstriction when using permanent microparticules [32]. However, there is no evidence that this approach is effective, especially for deeper tissues such as bone and nerves. In the current study, no non-target embolizations were reported suggesting that the rapid arterial recanalization ensured by the use of this emulsion is key to explaining this good safety profile. Indeed, the temporary embolic properties of ethiodized oil-based emulsions have been widely demonstrated in the treatment of primary liver cancer by conventional transarterial chemoembolization [20]. Moreover, the "showering" effect of transient GAE is fully in line with the TAME concept initially proposed by Okuno et al. to treat painful joints [14].

For conventional transarterial chemoembolization, a stable water-in-oil emulsion is produced by continuous pumping of water-soluble chemotherapy into pure ethiodized oil [20]. Typically, the emulsion is injected through a microcatheter and creates small radiopaque droplets that progressively slow down the arterial flow, up to total occlusion. A few minutes later, the flow reappears and sequential repeated sessions of conventional transarterial chemoembolization can be repeated via the same route, thanks to the temporary nature of this arterial occlusion. Because there is no need for chemotherapy in GAE, we designed and patented (WO2022/123049) this emulsion made of water-soluble contrast agent and ethiodized oil in a proportion that was optimized in the research lab. Before designing this first-in-human study, we conducted an *in vivo* preclinical study (unpublished personal data) in which we confirmed that this emulsion was able to temporarily embolize (10 min) the arteries (kidney, knee, shoulder, and rete mirabile). The safety profile was also good since we did not observe any skin/tendon/bone damage.

Table 4
Responders and patients reaching acceptable symptom state at follow-up.

Variable	1 week	1 month	3 months
Responders*			
Kellgren-Lawrence score			
All	16 (16/22; 73%)	16 (16/21; 76%)	16 (16/22; 73%)
3	9 (9/10; 90%)	9 (9/10; 90%)	8 (8/10; 80%)
4	7 (7/12; 58%)	7 (7/11; 64%)	8 (8/12; 67%)
Patients with acceptable symptom state†	10 (10/22; 45%)	9 (9/21; 43%)	9 (9/22; 41%)

Variables are expressed as raw numbers followed by proportions and percentages into parentheses.
VAS indicates Visual analog scale; WOMAC indicates Western Ontario and McMaster Universities Osteoarthritis Index; OMERACT indicates outcome measures in rheumatoid arthritis clinical trials; OARSI indicates Osteoarthritis Research Society.
* OMERACT-OARSI set of responder criteria including high improvement in pain or in WOMAC function (relative change ≤−50% and absolute change ≤−20) or improvement in pain and in WOMAC function (relative change ≤ −20% and absolute change ≤−10) [27].
† VAS pain score < 32.3 mm [28].

In this study, a marked clinical benefit, with improvement in VAS pain, WOMAC index and WOMAC function scores was described in participants with moderate to severe KOA (KL grade 3–4). On a per-patient basis, 73% of the participants could be classified as responders using the OMERACT-OARSI set of responders' criteria, and 41% were asymptomatic at three months. Bagla et al. described similar improvement in both pain and WOMAC global scores despite the participants having less severe KOA (KL grade 1–3) [16]. In the Genesis trial, mean pain improvement was lower than ours despite less severe KOA (KL grade 1–3) [18]. In our study, clinical improvement was observed in participants with severe KOA (KL grade 4) whereas these patients are often excluded from trials, probably because it is assumed that GAE would be ineffective in these patients with impaired cartilage. Indeed, Lee et al. reported a non-significant improvement in pain score for participants with KL grade 4 [17].

The main limitations of the study are the small number of participants, the absence of a comparative group with random treatment allocation and short follow-up. In addition, our study was designed to focus on safety and the findings on efficacy should be interpreted with caution.

In conclusion, GAE using an ethiodized oil-based emulsion is safe, reduces pain and improves knee function in participants with painful KOA for at least three months. This embolic agent appears to be a favorable option by comparison with permanent microparticles or imipenem/cilastatin that both have limitations. If our results are confirmed in larger, randomized, controlled trials, ethiodized oil-based emulsion could become one option for GAE.

Human rights

The authors declare that the work described has been performed in accordance with the Declaration of Helsinki of the World Medical Association revised in 2013 for experiments involving humans.

Informed consent and patient details

The authors declare that this report does not contain any personal information that could lead to the identification of the patients.

Author contributions

All authors attest that they meet the current International Committee of Medical Journal Editors (ICMJE) criteria for Authorship.

Declaration of Competing Interest

MS reports consulting fees from Guerbet France and to be a co-inventor of the patented emulsion. OP and CD are also co-inventors of the patented emulsion. The other authors have no conflicts of interest related to this work to declare.

CRediT authorship contribution statement

Marc Sapoval: Conceptualization, Funding acquisition, Investigation, Supervision, Writing – original draft. **Charles Querub:** Investigation, Writing – review & editing. **Helena Pereira:** Methodology, Validation, Formal analysis, Data curation, Writing – original draft. **Olivier Pellerin:** Investigation, Writing – review & editing. **Tom Boeken:** Investigation, Writing – review & editing. **Alessandro Di Gaeta:** Investigation, Writing – review & editing. **Marc Al Ahmar:** Investigation, Writing – review & editing. **Marie-Martine Lefevre-Colau:** Investigation, Writing – review & editing. **Christelle Nguyen:** Investigation, Writing – review & editing. **Camille Daste:** Investigation, Writing – review & editing. **Maxime Lacroix:** Investigation, Writing – review & editing. **Jean-Denis Laredo:** Investigation, Writing – review & editing. **Brigitte Sabatier:** Investigation, Writing – review & editing. **Nicolas Martelli:** Investigation, Writing – review & editing. **Gilles Chatellier:** Methodology, Writing – review & editing. **Carole Déan:** Conceptualization, Funding acquisition, Project administration, Writing – original draft. **François Rannou:** Conceptualization, Investigation, Writing – review & editing.

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References

[1] Cui A, Li H, Wang D, Zhong J, Chen Y, Lu H. Global, regional prevalence, incidence and risk factors of knee osteoarthritis in population-based studies. EClinicalMedicine 2020;29–30:100587.
[2] Bortoluzzi A, Furini F, Scirè CA. Osteoarthritis and its management: epidemiology, nutritional aspects and environmental factors. Autoimmun Rev 2018;17:1097–104.
[3] Mabey T, Honsawek S. Cytokines as biochemical markers for knee osteoarthritis. World J Orthop 2015;6:95–105.
[4] Nelson AE. Osteoarthritis year in review 2017: clinical. Osteoarthr Cartil 2018;26:319–25.
[5] March L, Smith EUR, Hoy DG, Cross MJ, Sanchez-Riera L, Blyth F, et al. Burden of disability due to musculoskeletal (MSK) disorders. Best Pract Res Clin Rheumatol 2014;28:353–66.
[6] Bannuru RR, Natov NS, Obadan IE, Price LL, Schmid CH, McAlindon TE. Therapeutic trajectory of hyaluronic acid versus corticosteroids in the treatment of knee osteoarthritis: a systematic review and meta-analysis. Arthritis Rheum 2009;61:1704–11.
[7] Ali SA, Kokorelias KM, MacDermid JC, Kloseck M. Education and social support as key factors in osteoarthritis management programs: a scoping review. Arthritis 2018;2018:2496190.
[8] Ahmed O, Block J, Mautner K, Plancher K, Anitescu M, Isaacson A, et al. Percutaneous management of osteoarthritis in the knee: proceedings from the Society of Interventional Radiology research consensus panel. J Vasc Interv Radiol 2021;32:919.e1–6.
[9] Hussain SM, Neilly DW, Baliga S, Patil S, Meek R. Knee osteoarthritis: a review of management options. Scott Med J 2016;61:7–16.
[10] Spiliopoulos S, Filippiadis D. Minimally invasive loco-regional treatments for painful knee osteoarthritis: the time has come. Diagn Interv Imaging 2021;102:651–2.
[11] Berenbaum F. Osteoarthritis as an inflammatory disease (osteoarthritis is not osteoarthrosis!). Osteoarthr Cartil 2013;21:16–21.
[12] Mapp PI, Walsh DA. Mechanisms and targets of angiogenesis and nerve growth in osteoarthritis. Nat Rev Rheumatol 2012;8:390.
[13] Ashraf S, Wibberley H, Mapp PI, Hill R, Wilson D, Walsh DA. Increased vascular penetration and nerve growth in the meniscus: a potential source of pain in osteoarthritis. Ann Rheum Dis 2011;70:523–9.
[14] Okuno Y, Matsumura N, Oguro S. Transcatheter arterial embolization using imipenem/cilastatin sodium for tendinopathy and enthesopathy refractory to nonsurgical management. J Vasc Interv Radiol 2013;24:787–92.
[15] Okuno Y, Korchi AM, Shinjo T, Kato S. Transcatheter arterial embolization as a treatment for medial knee pain in patients with mild to moderate osteoarthritis. Cardiovasc Intervent Radiol 2015;38:336–43.
[16] Bagla S, Piechowiak R, Hartman T, Orlando J, Del Gaizo D, Isaacson A. Genicular artery embolization for the treatment of knee pain secondary to osteoarthritis. J Vasc Interv Radiol 2020;31:1096–102.
[17] Lee SH, Hwang JH, Kim DH, So YH, Park J, Cho SB, et al. Clinical outcomes of transcatheter arterial embolisation for chronic knee pain: mild-to-moderate versus severe knee osteoarthritis. Cardiovasc Intervent Radiol 2019;42:1530–6.
[18] Little M, Gibson M, Briggs J, Speirs A, Yoong P, Ariyanayagam T, et al. Genicular artery embolization in patients with osteoarthritis of the knee (GENESIS) using permanent microspheres: interim analysis. Cardiovasc Intervent Radiol 2021;44:1–10.
[19] Casadaban LC, Mandell JC, Epelboym Y. Genicular artery embolization for osteoarthritis related knee pain: a systematic review and qualitative analysis of clinical outcomes. Cardiovasc Intervent Radiol 2020;44:1–9.

[20] Deschamps F, Moine L, Isoardo T, Tselikas L, Paci A, Mir LM, et al. Parameters for stable water-in-oil Lipiodol emulsion for liver transarterial chemo-embolization. Cardiovasc Intervent Radiol 2017;40:1927–32.
[21] Querub C, Ahmar MA, Boeken T, Gaeta AD, Pellerin O, Sapoval M. Embolic decision making in musculoskeletal embolization. Tech Vasc Interv Rad 2023;26:100879.
[22] Verhaeghe L, Holsbeeck AV, Bonne L, Claus E, Marrannes J, Vandenbulcke R, et al. Therapeutic lymphangiography with ethiodized oil for the management of lymphoceles and chylous ascites. Diagn Interv Imaging 2023;104:500–5.
[23] Altman R, Asch E, Bloch D, Bole G, Borenstein D, Brandt K, et al. Development of criteria for the classification and reporting of osteoarthritis: classification of osteoarthritis of the knee. Arthritis Rheum 1986;29:1039–49.
[24] Kohn MD, Sassoon AA, Fernando ND. Classifications in brief: Kellgren-Lawrence classification of osteoarthritis. Clin Orthop Relat Res 2016;474:1886–93.
[25] Jordan KM. EULAR recommendations 2003: an evidence based approach to the management of knee osteoarthritis: report of a task force of the Standing Committee for International Clinical Studies Including Therapeutic Trials (ESCISIT). Ann Rheum Dis 2003;62:1145–55.
[26] Bellamy N, Buchanan WW, Goldsmith CH, Campbell J, Stitt LW. Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. J Rheumatol 1988;15:1833–40.
[27] Pham T, Van Der Heijde D, Lassere M, Altman RD, Anderson JJ, Bellamy N, et al. Outcome variables for osteoarthritis clinical trials: the OMERACT-OARSI set of responder criteria. J Rheumatol 2003;30:1648–54.
[28] Tubach F, Ravaud P, Baron G, Falissard B, Logeart I, Bellamy N, et al. Evaluation of clinically relevant states in patient reported outcomes in knee and hip osteoarthritis: the patient acceptable symptom state. Ann Rheum Dis 2005;64:34–7.
[29] Khalilzadeh O, Baerlocher MO, Shyn PB, Connolly BL, Devane AM, Morris CS, et al. Proposal of a new adverse event classification by the Society of Interventional Radiology standards of practice committee. J Vasc Interv Radiol 2017;28:1432–7 e3.
[30] Barat M, Jannot AS, Dohan A, Soyer P. How to report and compare quantitative variables in a radiology article. Diagn Interv Imaging 2022;103:571–3.
[31] Torkian P, Golzarian J, Chalian M, Clayton A, Rahimi-Dehgolan S, Tabibian E, et al. Osteoarthritis-related knee pain treated with genicular artery embolization: a systematic review and meta-analysis. Orthop J Sports Med 2021;9:23259671211021356.
[32] Padia SA, Genshaft S, Blumstein G, Plotnik A, Kim GHJ, Gilbert SJ, et al. Genicular artery embolization for the treatment of symptomatic knee osteoarthritis. JB JS Open Access 2021;6:e21. 00085.