

Does Adjunction of Autologous Osteoblastic Cells Improve the Results of Core Decompression in Early-stage Femoral Head Osteonecrosis? A Double-blind, Randomized Trial

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Abstract

Background Osteonecrosis of the femoral head (ONFH) is a disabling disease that can ultimately progress to collapse of the femoral head, often resulting in THA. Core

decompression of the femoral head combined with cell therapies have shown beneficial effects in previous clinical studies in patients with early-stage (Association Research

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Ethical approval for this study was obtained from CUB-ULB Erasme, Brussels, Belgium (BE01); Universitätsklinikum Köln, Köln, Germany (DE02); CHU Saint-Etienne – Comité de Protection des Personnes Sud-est 1, France (FR01); NRES Committee London – West London and GTAC, UK (UK01); and Centrale Commissie Mensgebonden Onderzoek, the Netherlands (NL01).

The study was registered at <http://www.clinicaltrials.gov> (NCT01529008).

This work was performed at 29 study centers: 10 in Belgium (CUB-ULB Hôpital Erasme, Brussels; CHU Saint-Pierre, Brussels; AZ Sint-Jan Brugge-Oostende, Oostende; AZ Delta, Roeselare; CHR Citadelle, Liège; ZNA Jan Palfijn, Merksem; UZ Gent, Ghent; AZ Groeninge, Kortrijk; AZ Maria Middelaers, Ghent; Jessa Ziekenhuis, Hasselt), seven in France (CHU Saint-Etienne – Hôpital Nord, Saint-Priest-en-Jarez; CHRU Nancy, Nancy; CHU Amiens – Hôpital Sud, Amiens; Hôpital Sud-Francilien, Corbeil-Essonnes; CHU Caen, Caen; Hôpital de la Cavale Blanche, Brest; CHRU Lille – Hôpital Roger Salengro, Lille), six in Germany (Orthopädische Klinik der Medizinischen Hochschule Hannover im Annastift, Hannover; Klinik und Poliklinik für Orthopädie und Unfallchirurgie – Uniklinik Köln, Cologne; Universität Würzburg Orthopädische Klinik im König-Ludwig Haus, Würzburg; Universitätsklinikum Carl Gustav Carus an der TU Dresden Klinik und Poliklinik für Orthopädie, Dresden; Universitätsmedizin Greifswald Körperschaft des öffentlichen Rechts Klinik und Poliklinik für Orthopädie und Orthopädische Chirurgie, Greifswald; Waldkrankenhaus “Rudolf Elle” GmbH, Eisenberg), four in the United Kingdom (Cambridge University Hospitals NHS Foundation Trust, Cambridge; University Hospital Southampton NHS Foundation Trust, Southampton; King’s College Hospital London NHS Foundation Trust, London; The Royal Orthopaedic Hospital NHS Foundation Trust, Birmingham), and two in the Netherlands (MC Erasmus, Rotterdam; UMC Utrecht, Utrecht).

Circulation Osseous [ARCO] Stage I and II) ONFH. However, high-quality evidence confirming the efficacy of this treatment modality is still lacking.

Questions/purposes (1) Is core decompression combined with autologous osteoblastic cell transplantation superior to core decompression with placebo implantation in relieving disease-associated pain and preventing radiologic ONFH progression in patients with nontraumatic early-stage ONFH? (2) What adverse events occurred in the treatment and control groups?

Methods This study was a Phase III, multicenter, randomized, double-blind, controlled study conducted from 2011 to 2019 (ClinicalTrials.gov registry number: NCT01529008). Adult patients with ARCO Stage I and II ONFH were randomized (1:1) to receive either core decompression with osteoblastic cell transplantation (5 mL with 20×10^6 cells/mL in the study group) or core decompression with placebo (5 mL of solution without cells in the control group) implantation. Thirty percent (68 of 230) of the screened patients were eligible for inclusion in the study; of these, 94% (64 of 68) underwent a bone marrow harvest or sham procedure (extended safety set) and 79% (54 of 68) were treated (study group: 25 patients; control group: 29). Forty-nine patients were included in the efficacy analyses. Similar proportions of patients in each group completed the study at 24 months of follow-up (study group: 44% [11 of 25]; control: 41% [12 of 29]). The study and control groups were comparable in

important ways; for example, in the study and control groups, most patients were men (79% [27 of 34] and 87% [26 of 30], respectively) and had ARCO Stage II ONFH (76% [19 of 25] and 83% [24 of 29], respectively); the mean age was 46 and 45 years in the study and control groups, respectively. The follow-up period was 24 months post-treatment. The primary efficacy endpoint was the composite treatment response at 24 months, comprising the clinical response (clinically important improvement in pain from baseline using the WOMAC VA3.1 pain subscale, defined as 10 mm on a 100-mm scale) and radiologic response (the absence of progression to fracture stage $\geq$ ARCO Stage III), as assessed by conventional radiography and MRI of the hips). Secondary efficacy endpoints included the percentages of patients achieving a composite treatment response, clinical response, and radiologic response at 12 months, and the percentage of patients undergoing THA at 24 months. We maintained a continuous reporting system for adverse events and serious adverse events related to the study treatment, bone marrow aspiration and sham procedure, or other study procedures throughout the study. A planned, unblinded interim analysis of efficacy and adverse events was completed at 12 months. The study was discontinued because our data safety monitoring board recommended terminating the study for futility based on preselected futility stopping rules: conditional power below 0.20 and $p = 0.01$ to detect an effect size of 10 mm on

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the 100-mm WOMAC VA3.1 pain subscale (improvement in pain) and the absence of progression to fracture ($\geq$ ARCO Stage III) observed on radiologic assessment, reflecting the unlikelihood that statistically beneficial results would be reached at 24 months after the treatment.

Results There was no difference between the study and control groups in the proportion of patients who achieved a composite treatment response at 24 months (61% [14 of 23] versus 69% [18 of 26]; $p = 0.54$). There was no difference in the proportion of patients with a treatment response at 12 months between the study and control groups (14 of 21 versus 15 of 23; $p = 0.92$), clinical response (17 of 21 versus 16 of 23; $p = 0.38$), and radiologic response (16 of 21 versus 18 of 23; $p = 0.87$). With the numbers available, at 24 months, there was no difference in the proportion of patients who underwent THA between the study and control groups (24% [six of 25] versus 14% [four of 29]). There were no serious adverse events related to the study treatment, and only one serious adverse event (procedural pain in the study group) was related to bone marrow aspiration. Nonserious adverse events related to the treatment were rare in the study and control groups (4% [one of 25] versus 14% [four of 29]). Nonserious adverse events related to bone marrow or sham aspiration were reported by 15% (five of 34) of patients in the study group and 7% (two of 30) of patients in the control group.

Conclusion Our study did not show any advantage of autologous osteoblastic cells to improve the results of core decompression in early-stage (precollapse) ONFH. Adverse events related to treatment were rare and generally mild in both groups, although there might have been a potential risk associated with cell expansion. Based on our findings, we do not recommend the combination of osteoblastic cells and core decompression in patients with early-stage ONFH. Further, well-designed studies should be conducted to explore whether other treatment modalities involving a biological approach could improve the overall results of core decompression.

Level of Evidence Level II, therapeutic study.

Introduction

Osteonecrosis of the femoral head (ONFH) is a disabling condition that mostly affects adults aged 30 to 50 years and more often affects men than women [29, 22, 3, 31, 40]. Without early intervention, progression to femoral head collapse is eventually observed in most patients; at this point, it is often treated with THA [29, 37]. Although the exact pathogenesis of nontraumatic ONFH remains unclear, risk factors include excessive corticosteroid use and alcohol intake, certain diseases, smoking, and obesity [47, 20, 28, 49, 40]. Staging of ONFH is based on the 2019 Association Research Circulation Osseous (ARCO) staging system, with four defined disease stages [45]. The main goals of early-stage ONFH (ARCO Stages I and II) treatment include

improvement in symptoms and function, preservation of the femoral head, and delay of the time until THA.

Current treatment options for these precollapse stages include numerous surgical procedures and nonsurgical management, including medications and biophysical treatments [29], but considerable disagreement remains about how to treat patients with precollapse ONFH. Core decompression is a widely accepted procedure for these patients, but it has inconsistent success [26]. This highlights the need to search for more effective therapeutic options in the management of precollapse ONFH. There has been growing interest in investigating whether core decompression combined with other treatments such as mesenchymal stem cells or osteoinductive agents can improve outcomes for patients with ONFH [28, 32]. Focal adjunction of mesenchymal stem cells is a particularly promising therapy for ONFH, given their ability to differentiate into specific cell lines and proliferate to repair damaged tissues [19]. Studies have suggested that core decompression combined with cell therapy (in vitro culture or concentrated autologous bone marrow-containing mononuclear cells) has beneficial effects in patients with early-stage ONFH [7, 8, 12, 13, 25, 30, 43, 48]. However, current data remain inconclusive [1], and the treatment is controversial.

We therefore asked: (1) Is core decompression combined with autologous osteoblastic cell transplantation superior to core decompression with placebo implantation in relieving disease-associated pain and preventing radiologic ONFH progression in patients with nontraumatic early-stage ONFH? (2) What adverse events occurred in the treatment and control groups?

Patients and Methods

Study Design, Setting, and Overview

This study was a Phase III, multicenter, randomized, double-blind controlled study conducted in Belgium, the Netherlands, France, Germany, and the United Kingdom between December 2011 and February 2019.

Patients were randomized (1:1) to receive either core decompression combined with osteoblastic cell transplantation (study group) or core decompression combined with placebo implantation (control group). Patients were screened up to 30 days before the bone marrow harvest (study group) or sham intervention (control group) for nontraumatic ONFH using conventional radiographs, CT, and MRI (Fig. 1).

The follow-up period was 24 months, with planned post-treatment assessments at 1, 3, 6, 12, 18, and 24 months of follow-up. Follow-up at 36 and 48 months post-treatment was planned to assess selected efficacy and safety parameters (Fig. 1).

An independent data safety monitoring board performed a planned, unblinded interim analysis of efficacy and adverse events when complete 12-month post-treatment follow-up

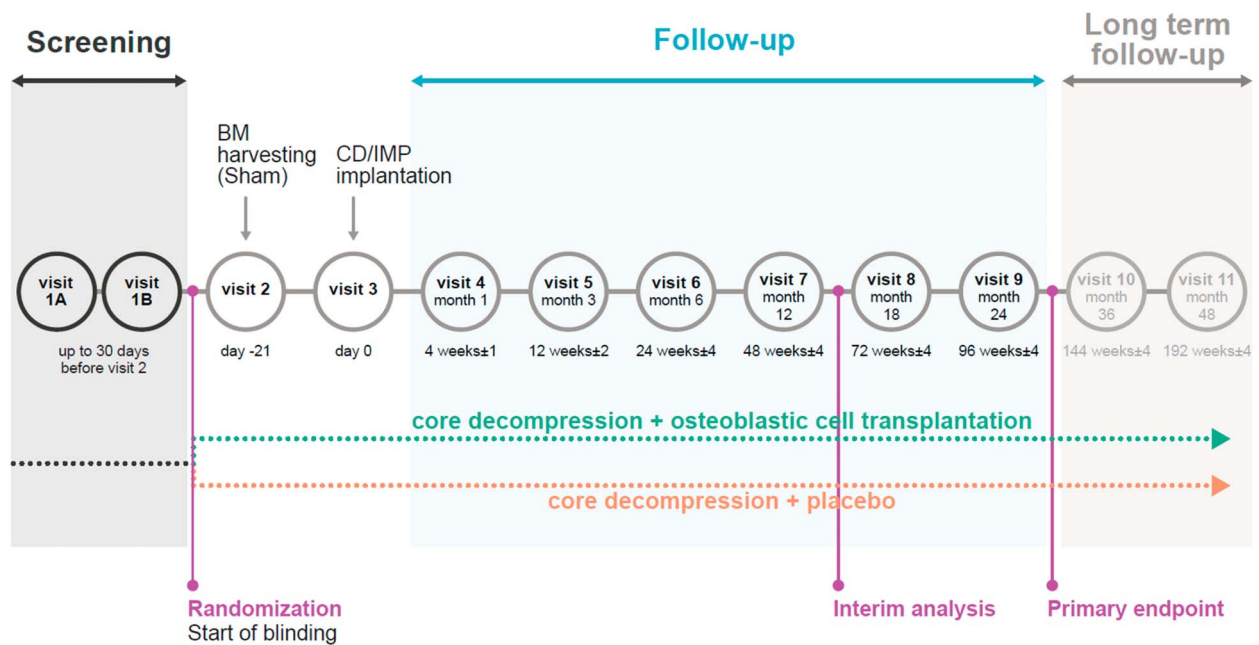


Fig. 1 This figure shows the study design. CD and osteoblastic cell transplantation (green arrow) = patients randomized to the study group (CD combined with autologous osteoblastic cell implantation). CD and placebo (orange arrow) = patients randomized to the control group (CD combined with placebo implantation). The purple lines indicate the start of randomization and the interim analysis at 12 months or the primary endpoint analysis. BM = bone marrow; CD = core decompression; IMP = investigational medicinal product.

data were available for approximately 40% of the initial target number of 110 patients (that is, 44 patients) in November 2018 (Fig. 1). The data safety monitoring board recommended terminating the study for futility based on preselected criteria, namely, conditional power below 0.20 and $p = 0.01$ to detect an effect size of 10 mm on a 100-mm WOMAC VA3.1 pain subscale (improvement in pain) and the absence of progression to fracture ($\geq$ ARCO Stage III) observed on radiologic assessment, reflecting the unlikelihood that statistically and significantly beneficial results would be reached at 24 months post-treatment. All patients in the interim analysis were followed until 24 months.

Study Participants

Eligible patients were men or women aged 18 to 70 years with a diagnosis of nontraumatic ONFH and ARCO Stages I or II (no fracture of the necrotic femoral head) ONFH on radiographs and MRI. Clinical, biological, and imaging data were obtained for eligible patients before inclusion. Radiographs and CT images of both hips were obtained according to each study center's imaging parameters. Baseline MRI examinations for all participants were performed according to a radiologic manual and included large field-of-view comparative coronal T1-SE and T2-SE sequence images and high-resolution sagittal T1-saturated and fat-saturated proton density-weighted

images. The necrotic angle representing the sum of the Kerboul angles (angle formed between the center of the femoral head and the extent of the ON lesion at the subchondral plate of the femoral head) was calculated for all target hips [9]. Symptomatic hips were defined by the presence of a pain scale ≥ 20 mm according to the WOMAC VA3.1 pain score, which was obtained within 48 hours before screening [5].

Patients were included if they had either symptomatic ARCO Stage I or II ONFH or asymptomatic ARCO Stage II ONFH with a necrotic angle $\geq 190^\circ$ (Table 1). Clinical data were assessed by onsite recruiting orthopaedists, and radiologic data were assessed by a central senior radiologist (BVB) before treatment. Patients were excluded if they had traumatic or hyperbaric ON, other bone marrow lesions, medical conditions interfering with an evaluation of pain in the studied hip, or other risk factors (such as hepatitis, HIV, or allergies related to the intervention). Patients previously treated with osteoblastic cell transplantation or core decompression of the hip within 6 months of screening were also excluded (Supplemental Digital Content 1; <http://links.lww.com/CORR/B48>).

Randomization and Blinding

Patients were randomized (1:1) to the treatment groups, and stratification according to ARCO stage was performed

Table 1. Inclusion criteria of ONFH

ARCO stage	Modified Kerboul angles ^a	Pain ^b
Stage I	$\geq 190^\circ$	≥ 20 mm ^c
Stage II	$< 190^\circ$	≥ 20 mm ^c
Stage II	$\geq 190^\circ$	≥ 20 mm or no pain ^c

^aSum of coronal and sagittal necrotic angles.

^bWOMAC VA3.1 pain during the 48 hours before screening.

^cOn a 100-mm scale. ONFH = osteonecrosis of the femoral head; ARCO = Association Research Circulation Osseous.

at the time of randomization. The study was conducted in a double-blind manner. Bone marrow harvesting or sham intervention was conducted by an independent physician in each institution who was not otherwise involved in any other study-related procedures; all other investigators and patients were blind to treatment assignment. The (sham) bone marrow harvest and core decompression with implantation procedures were identical for all patients. The treatment was supplied in identical packaging conditions. All images (conventional radiographs, MRI, and CT) were processed in a manner that ensured blinding (Supplemental Digital Content 1; <http://links.lww.com/CORR/B48>).

Study Population

Thirty percent of the screened patients (68 of 230) were eligible and included in the study between December 2011 and February 2019. The main reason for exclusion was the presence of ARCO Stage $\geq$ III ONFH (in 58% [133 of 230] of patients). Of the included patients, 94% (64 of 68) underwent a bone marrow harvest or sham procedure (study group: 34 patients; control group: 30 patients) and were included in the extended safety set. Seventy-nine percent (54 of 68) of patients underwent core decompression combined with osteoblastic cell transplantation or placebo implantation (study group: 25 patients; control group: 29 patients) (Fig. 2). Of the treated patients, 92% (23 of 25) of those in the study group and 90% (26 of 29) of those in the control group were included in the primary efficacy analysis (full analysis set). One patient was randomized to the study group but accidentally underwent sham bone marrow harvesting. Three patients randomized to the control group did not undergo sham bone marrow harvesting because they withdrew their consent to participate or because of the investigator's decision. These patients were not treated and were excluded from all analysis sets (Fig. 2).

Similar proportions of patients in each group completed the study until 24 months after implantation (study group: 44% [11 of 25]; control group: 41% [12 of 29]). Twenty-five patients discontinued the study before 24 months because of the sponsor's decision to terminate the study for futility (Fig. 2). The mean duration of post-treatment

follow-up was 17 ± 8 months (range 0 to 26 months) in the study group and 18 ± 7 months (range 3 to 24 months) in the control group (Supplemental Digital Content 2; <http://links.lww.com/CORR/B49>).

The mean patient age at screening was 46 years $\pm$ 10 years (range 30 to 62 years) in the study group and 45 $\pm$ 10 years (range 31 to 68 years) in the control group. In both groups, most patients were men (study group: 79% [27 of 34]; control group: 87% [26 of 30]) and White (study group: 88% [30 of 34]; control group: 97% [29 of 30]; of note, the ethnic origin of the patient was identified by the investigator or data nurse based on observation or information provided by the patient) (Table 2). More patients in the control group consumed alcohol and smoked tobacco than did those in the study group (80% [24 of 30] versus 38% [13 of 34] and 87% [26 of 30] versus 47% [16 of 34], respectively). The WOMAC total score, WOMAC pain subscale score, and mean necrotic angle were comparable between the study and control groups. ARCO Stage II ONFH was diagnosed in 76% (19 of 25) of patients in the study group and 83% (24 of 29) of patients in the control group (Table 2) (Supplemental Digital Content 3; <http://links.lww.com/CORR/B50>).

Treatment

PREOB (Bone Therapeutics SA, currently BioSonic SA) is a fresh cell suspension of human autologous bone marrow–derived osteoblastic cells. Bone marrow (between 30 and 50 mL) was harvested from the patient's hip (iliac crest) under local anesthesia. Bone marrow coagulation was prevented by the addition of heparin. Bone marrow was then transported at room temperature to the manufacturing site (24-hour stability of bone marrow at room temperature has been established [10]).

Mononuclear cells were isolated from bone marrow using density (FicollTM) gradient centrifugation. The cells were then plated and cultured ex vivo in a culture medium containing specific growth factors triggering differentiation toward osteoblastic lineage under strictly controlled conditions and according to good manufacturing practice guidelines.

As described [6, 11], the mesenchymal profile and osteoblastic character of cells were controlled by flow cytometry. The mesenchymal phenotype was defined as the expression level of specific mesenchymal stem cell markers such as CD105, CD73, and CD90 of at least 80%, while being negative ($< 5\%$) for hematopoietic stem cell markers (CD45, CD19, and CD14). The osteoblastic character was determined by measuring the CD166 expression and enzymatic activity of alkaline phosphatase. In addition, cells were considered ready for use if the culture had good cell viability ($> 70\%$) and a sufficient cell count (planned dose: 20×10^6 cells) and passed the sterility test (gram staining and endotoxin measurement) and mycoplasma testing.

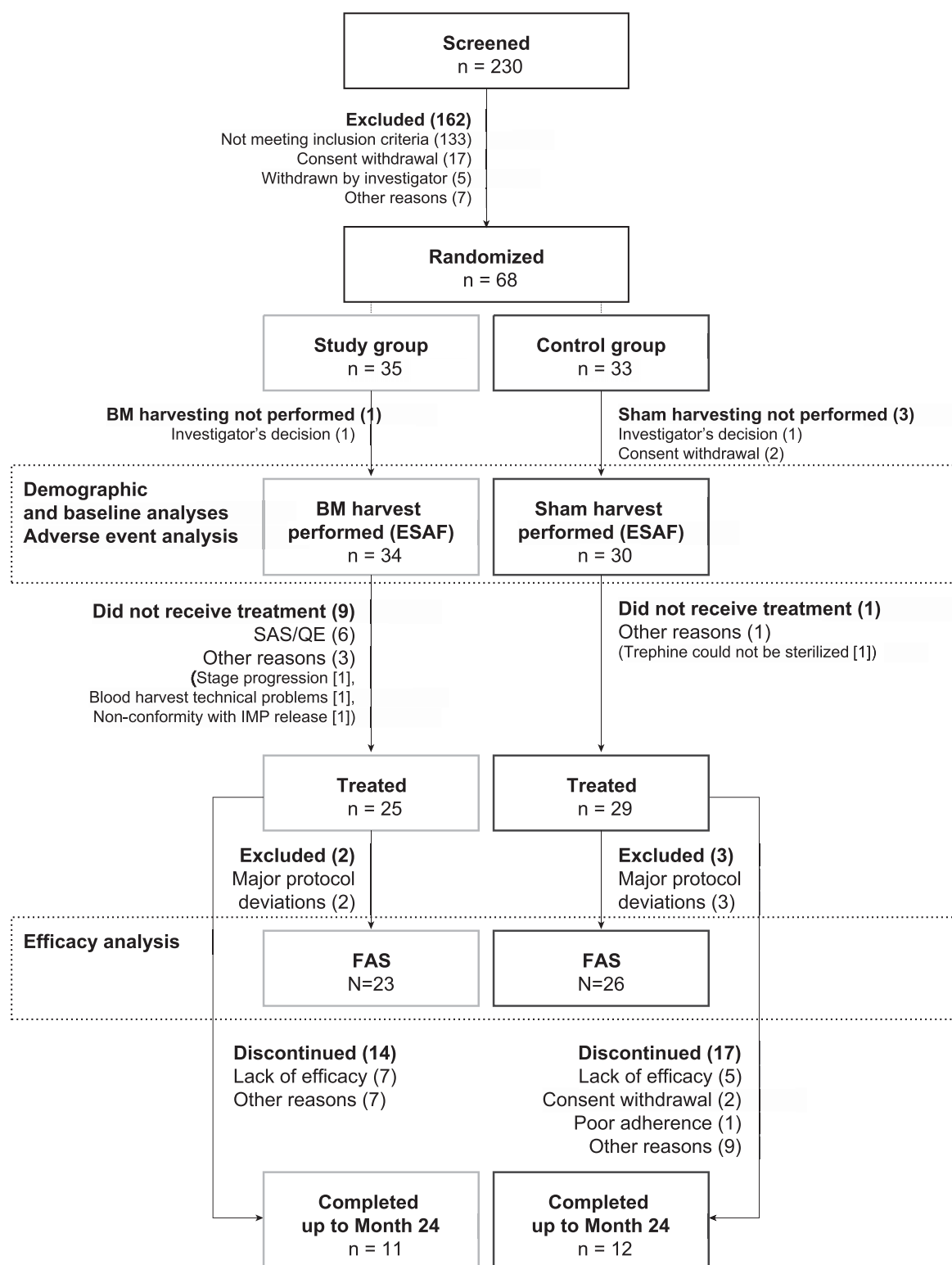


Fig. 2 This flowchart shows the patients who were included in this trial. Study group: patients treated with core decompression and autologous osteoblastic cell transplantation; control group: patients treated with core decompression and placebo implantation. ESAF = extended safety set; FAS = full analysis set; IMP = investigational medicinal product; BM = bone marrow; SAS/QE = serious adverse safety/quality event.

Table 2. Baseline demographic and clinical characteristics of the study patients

Characteristic	Study group (n = 34)	Control group (n = 30)
Men, % (n)	79 (27)	87 (26)
Age in years, mean $\pm$ SD	46 $\pm$ 10	45 $\pm$ 10
Ethnic origin ^a , % (n)		
White	88 (30)	97 (29)
Black	6 (2)	3 (1)
Asian	3 (1)	0 (0)
Other	3 (1)	0 (0)
Use of glucocorticoids, % (n)	18 (6)	23 (7)
Alcohol consumption, % (n)	38 (13)	80 (24)
Smoking, % (n)	47 (16)	87 (26)
Clinical evaluation of the treated hip	Study group (n = 25)^b	Control group (n = 29)^b
WOMAC total score, mean $\pm$ SD	41 $\pm$ 23	37 $\pm$ 28
WOMAC pain subscale score, mean $\pm$ SD	42 $\pm$ 23	37 $\pm$ 29
Radiologic evaluation of the treated hip	Study group (n = 25)^b	Control group (n = 29)^b
Combined necrotic angle of Kerboul in $^{\circ}$		
n	23	27
mean $\pm$ SD	266 $\pm$ 85	255 $\pm$ 102
ARCO classification ^c		
n	25	29
Stage I, % (n)	20 (5)	10 (3)
Stage II, % (n)	76 (19)	83 (24)
Stage III, % (n)	4 (1)	0 (0)
Stage IV, % (n)	0 (0)	7 (2)

Because of rounding, some percentages do not add up to 100%.

^aThe ethnic origin of the patients was identified by the principal investigator or the study data nurse based on observation or information provided by the patient.

^bData were collected only in treated patients.

^cAdjudicated ARCO classification for patients included in the interim analysis; classification was performed by the independent radiologist for the remaining patients. ARCO = Association Research Circulation Osseous; n = total number of patients; % (n) = percentage (number) of patients within a category; SD = standard deviation.

Three weeks after cell harvesting, osteoblastic cells were provided to the treating surgeon as a cell suspension in prefilled, single-dose, noncryopreserved (15° to 25°C), ready-to-use syringes containing cell suspension (20×10^6 cells) in 5 mL of phosphate-buffered saline and human serum albumin (20%).

A placebo was provided in a single-dose, ready-to-use syringe containing a 5-mL solution of phosphate-buffered saline and human serum albumin. Patients underwent fluoroscopically guided core decompression via a small-diameter (5-mm) trephine under general anesthesia (Supplemental Digital Content 4; <http://links.lww.com/CORR/B51>). In addition, using the same trephine, the surgeon implanted the patients with a single 5-mL dose of either the osteoblastic cell suspension or placebo in the necrotic lesion. To avoid any

leakage, a piece of gel foam (Gelfoam, Pfizer) or equivalent was pushed through the trephine to close the hole. After core decompression and implantation, all patients were advised to remain nonweightbearing on the operated-on leg for 1 to 3 weeks. Thereafter, complete weightbearing was permitted. No specific rehabilitation procedure was conducted, and patients were allowed to progressively mobilize the hip without any physiotherapy. Stitches (if any) were removed 7 to 14 days after surgery per the standard of care.

Study Objectives and Outcome Measures

The main objective of this study was to demonstrate that core decompression combined with osteoblastic cell

transplantation into a necrotic lesion was superior to core decompression combined with placebo in relieving hip symptoms and halting (or reversing) radiologic progression to fracture stages ($\geq$ ARCO Stage III) in patients with nontraumatic early-stage ONFH at 24 months.

The primary efficacy endpoint was the percentage of patients who responded to treatment at 24 months. A treatment responder was defined as a patient who achieved both a clinical response and radiologic response. A clinical response was regarded as improvement in pain from baseline by at least the minimum clinically important difference (10 mm), assessed using the WOMAC VA3.1 (VAS subscale score of the treated hip) [5] (patients with a baseline WOMAC VA3.1 pain subscale score < 10 mm were considered responders if the score for the treated hip was between 0 and 4 mm, based on a published recommendation [15]). A radiologic response was considered a lack of progression to fracture ($\geq$ ARCO Stage III) in the treated hip, assessed at the studied timepoints using radiographs.

The secondary efficacy endpoints included the percentage of patients with a treatment response at 12 months, percentage of patients with a clinical response at 12 months, percentage of patients with a radiologic response at 12 months, and the percentage of patients undergoing THA for the study-treated hip at 24 months.

In addition, absolute changes in the WOMAC total score and WOMAC pain subscale scores of the treated hip from baseline to 12 months were assessed. Safety endpoints included the reporting of adverse events and serious adverse events throughout the study period (Supplemental Digital Content 5; <http://links.lww.com/CORR/B52>).

Data Collection and Analysis

The following information was gathered at screening (Visit 1): baseline demographic and disease characteristics (Supplemental Digital Content 6; <http://links.lww.com/CORR/B53>); laboratory tests for viral serology, hematology, and biochemistry; physical examination; vital signs (Supplemental Digital Content 7; <http://links.lww.com/CORR/B54>); and previous and concomitant medications. In addition, changes in health status, concomitant medication, physical examination, vital signs, and laboratory blood test results were also assessed at other study visits.

During the bone marrow harvest visit (Visit 2), patients in the study group had ≥ 50 mL of bone marrow aspirated for cell culture. Patients in the control group underwent a sham procedure to ensure the patient was blinded to the group assignment. Peripheral blood was collected for osteoblastic cell production (300 mL in the study group) or research (30 mL in the control group) (Supplemental Digital Content 4; <http://links.lww.com/CORR/B51>). After the procedure and 30 minutes after vital signs were checked, patients could leave

the hospital. Bone marrow harvesting was performed by an independent physician specific to each center.

At the third visit (Day 0), patients underwent core decompression combined with implantation. Patients in the study group received 5 mL of suspension containing osteoblastic cells, and patients in the control group received an injection of 5 mL of a cell-free solution (placebo). The osteoblastic cell suspension and placebo were visually similar and indistinguishable by the treating physician.

Efficacy Assessments

During the study, ARCO staging and Kerboul angle were determined based on follow-up radiographs and MRI by an independent, blinded radiologist (BVB) to assess the development of fracture and changes in lesion size [9]. In 2018, initial and follow-up radiographs (obtained at 6, 12, 18, and 24 months) and MR images (obtained at 6, 12, and 24 months) of the target hips were analyzed by two radiologists (the radiologist who participated in the patient inclusion process and another experienced musculoskeletal radiologist) who were blinded to all data to stage the lesions and determine necrotic angles. A consensus reading was performed in case of discrepancy. The interobserver reliability and reproducibility of ARCO staging for MRI and radiographs were determined. Intrareader reliability was defined as the degree of agreement (expressed as a percentage) among repeated measurements performed by the same reader (Supplemental Digital Content 8; <http://links.lww.com/CORR/B55>).

A chart review process was established to ensure data quality, anonymization, and blinding.

Adverse Events

Adverse events and serious adverse events were assessed from the time of patient enrollment until the last visit (Supplemental Digital Content 9; <http://links.lww.com/CORR/B56>).

An adverse event was defined as any negative medical occurrence that did not necessarily have a causal relationship with the study treatment. A serious adverse event was defined as any adverse event that was life-threatening or resulted in death, hospitalization or prolongation of current hospitalization, persistent or significant incapacity, substantial disruption of a patient's ability to conduct normal life activities, or congenital anomalies or birth defects.

Adverse events that started before the date of core decompression with implantation were not considered to be related to the treatment. Adverse events and serious adverse events that started on or after the date of core decompression with implantation (or if the start date of the

adverse event or serious adverse event or the start date of core decompression with implantation was missing or unknown) were considered treatment-related adverse events or serious adverse events.

The causal relationship between an adverse event or serious adverse event and the study treatment was assessed. Treatment-related adverse events were adverse events for which the investigator answered “Yes” to a relationship with the study treatment or adverse events with a missing relationship with the study treatment. Adverse events were classified as having a “certain,” “probable or likely,” “possible,” “conditional or unclassified,” or “not assessable or unclassifiable” causal relationship with bone marrow aspiration (sham) intervention, or as having “no relationship” with the bone marrow aspiration (sham) intervention. Adverse events related to other study procedures were those classified as having a “certain,” “probable or likely,” “possible,” “conditional or unclassified,” or “not assessable or unclassifiable” causal relationship with study procedures other than bone marrow aspiration and sham intervention (that is, anesthesia, blood sampling, and cell implantation) or those that had a missing relationship with study procedures other than bone marrow (sham) aspiration. Regular physical examinations were made, and vital signs, including heart rate, blood pressure, body temperature, and respiratory rate, were assessed at the follow-up timepoints. In addition, serology and biochemical and hematologic parameters were evaluated (Supplemental Digital Content 7; <http://links.lww.com/CORR/B54>).

Ethical Approval

We obtained ethical review board approval for this study. This trial was registered at ClinicalTrials.gov (NCT01529008).

Statistical Analyses

Based on internal datasets from a Phase IIB study, we assumed that 63% of patients in the study group and 30% in the control group would respond to treatment. Using a chi-square test, we planned a sample size test with a two-sided 5% significance level and a power of 90% to detect an effect size of 10 mm on a 100-mm WOMAC VA3.1 pain subscale (improvement in pain) and the absence of progression to fracture ($\geq$ ARCO Stage III) observed on radiologic assessment. Because the interim analysis was performed using a group sequential-design approach, the maximum sample size was increased to achieve the desired power of 90% at the final analysis. This increase depended on the overall significance level, statistical power, number of interim analyses, and type of

boundaries being used. To attain the desired power of 90% at the final analysis, and assuming a dropout rate of 7.5%, the overall sample size was estimated to be 118 patients (59 patients per group) to ensure 110 assessable patients at 24 months.

Three analysis sets were defined: The extended safety set included patients who underwent bone marrow harvesting, the safety set included all treated patients, and the full analysis set was a modified intention-to-treat population that included all randomized and treated patients with a baseline value and at least one post-baseline value available for both the ARCO stage and WOMAC pain subscale score for the study-treated hip and whose eligibility was confirmed after adjudication.

Efficacy was analyzed for the full analysis set at 24 months (Supplemental Digital Content 10; <http://links.lww.com/CORR/B57>).

No subgroup analyses such as analysis by gender were planned in the study protocol and were not performed.

Continuous data are described using the number of observations, mean, 95% confidence interval (CI), and standard deviation. Categorical data are described as the percentage of patients, numerator with denominator, and 95% CI.

The percentage of patients fulfilling the criteria for treatment response of the study-treated hip at 24 months (primary efficacy endpoint) was obtained after applying the rules for replacing post-baseline missing data (Supplemental Digital Content 10; <http://links.lww.com/CORR/B57>). All statistical analyses were performed using SAS software (SAS Institute) version 9.2 or later.

Results

Treatment Efficacy

Primary Efficacy Endpoint

There was no difference in the proportion of patients who achieved a composite successful treatment response between the study and control groups (clinical and radiologic) at 24 months (61% [14 of 23] [95% CI 39 to 80] versus 69% [18 of 26] [95% CI 48 to 86]; $p = 0.54$) (Table 3).

Secondary Efficacy Endpoints

There was no difference between the study and control groups in the proportion of patients with a successful treatment response at 12 months (14 of 21 versus 15 of 23; $p = 0.92$) (Table 4).

At 12 months, there were no differences in the proportions of patients with a clinical response between the study and control groups (17 of 21 versus 16 of 23; $p = 0.38$), nor

Table 3. Percentage of patients achieving successful composite treatment response at 12 and 24 months (full analysis set)

Overall success	Study group		Control group		Relative Risk (95% CI)	p value ^a
	n	% (n)	n	% (n)		
12 months	21	67 (14)	23	65 (15)	1.02 (0.67 to 1.56)	0.92
24 months ^b	23	61 (14)	26	69 (18)	0.88 (0.58 to 1.33)	0.54

Study group: patients treated with core decompression and implantation of autologous osteoblastic cells. Control group: patients treated with core decompression and placebo implantation. Twelve-month data were obtained for 44 patients included in the interim analysis and after applying the rules for missing data imputation. Data at 24 months were obtained for 49 patients included in the primary endpoint analysis (after terminating the study) and after applying the rules for missing data imputation. Overall success was defined as a composite of clinical success (improvement in pain from baseline by at least the minimum clinically important difference [10 mm], assessed using the WOMAC VA3.1 [VAS subscale score of the treated hip]; patients with a baseline WOMAC VA3.1 pain subscale score < 10 mm were considered responders if the score for the treated hip was between 0 and 4 mm) and radiologic success (lack of progression to fracture [≥ ARCO Stage III] in the treated hip, assessed at the studied timepoints using radiographs). The full analysis set was defined as a modified intention-to-treat cohort that included all randomized and treated patients, with a baseline value available of the ARCO stage and the WOMAC VA3.1 pain subscale score, and at least one post-baseline value available of both the ARCO stage and the WOMAC VA3.1 pain subscale score.

^aPearson chi-square test or Fisher exact test.

^bPrimary study endpoint.

n = number of evaluable patients; % (n) = percentage (number) of patients achieving overall success; CI = confidence interval.

was there a difference in the radiologic response (16 of 21 versus 18 of 23; $p = 0.87$) (Table 4).

With the numbers available, there was no difference in the proportion of patients who underwent THA for the study-treated hip until the end of follow-up between the study and control groups (24% [six of 25] versus 14% [four of 29]). Overall, at 2 years, the survival of patients who did not undergo THA was 82% (44 of 54). There were no differences between groups in treatment response at Month 24 when considering the effects of missing data (Supplemental Digital Content 11; <http://links.lww.com/CORR/B58>). There were also no differences between groups in the percentages of patients with radiologic progression at 12 months (Supplemental Digital Content 12; <http://links.lww.com/CORR/B59>), and in mean changes in the

WOMAC total and pain subscale scores from baseline to 12 months (Supplemental Digital Content 13; <http://links.lww.com/CORR/B60>).

Adverse Events

None of the treatment-related serious adverse events were considered related to treatment, and one treatment-related serious adverse event (procedural pain in a patient in the study group) was related to bone marrow or sham aspiration; no deaths were reported in either group (Table 5).

Nonserious treatment-related adverse events were rare in the study group (4% [one of 25] with systemic inflammatory response syndrome) and control group (14%

Table 4. Percentage of patients achieving a successful clinical and radiologic treatment response at 12 months (full analysis set)

	Study group			Control group			Absolute difference (study group minus control)	
	n	% (n)	95% CI	n	% (n)	95% CI	Value (95% CI)	p value ^a
Clinical success	21	81 (17)	58 to 95	23	70 (16)	47 to 87	-0.11 (-0.37 to 0.14)	0.38
Radiologic success	21	76 (16)	53 to 92	23	78 (18)	56 to 93	0.02 (-0.23 to 0.27)	0.87

Study group: patients treated with core decompression and implantation of autologous osteoblastic cells. Control group: patients treated with core decompression and placebo implantation. Data at 12 months were obtained for 44 patients included in the interim analysis and after applying the rules for missing data imputation. Clinical success was defined as improvement in pain from baseline by at least the minimum clinically important difference (10 mm), assessed using the WOMAC VA3.1 (VAS subscale score of the treated hip; patients with a baseline WOMAC VA3.1 pain subscale score < 10 mm were considered responders if the score for the treated hip was between 0 and 4 mm). Radiologic success was considered a lack of progression to fracture (≥ ARCO Stage III) in the treated hip, assessed at the studied timepoints using radiographs. The full analysis set was defined as a modified intention-to-treat cohort that included all randomized and treated patients, with a baseline value available of the ARCO stage and the WOMAC VA3.1 pain subscale score, and at least one post-baseline value available of both the ARCO stage and the WOMAC VA3.1 pain subscale score.

^aPearson chi-square test or Fisher exact test.

n = number of evaluable patients; % (n) = percentage (number) of patients with a response; CI = confidence interval.

Table 5. Overview of treatment-emergent adverse events related to treatment or study procedures

	Study group	Control group
Serious adverse events related to treatment	0 (0 of 25)	0 (0 of 29)
Adverse events related to treatment	4 (1 of 25)	14 (4 of 29)
Adverse events related to other study procedures	24 (8 of 34)	40 (12 of 30)
Adverse events related to BM or sham aspiration	15 (5 of 34)	7 (2 of 30)

Data are presented as % (n of n). Study group: patients treated with core decompression and implantation of autologous osteoblastic cells. Control group: patients treated with core decompression and placebo implantation. Data are reported for the safety set (all treated patients [n = 54]) or extended safety set (all patients undergoing harvesting [n = 64]). BM = bone marrow.

[four of 29] with systemic inflammatory response syndrome) (safety set, that is, all treated patients; n = 54) (Table 5). For the one patient in the study group who experienced systemic inflammatory response syndrome, the event started 2 days after osteoblastic cell transplantation and persisted for 33 days; thereafter, the patient recovered without treatment. All these events were nonserious and mild or moderate in severity. Treatment-related adverse events related to other study procedures (anesthesia, blood sampling, and cell implantation) were reported by 24% (eight of 34) of patients in the study group and 40% (12 of 30) of patients in the control group (extended safety set, that is, all patients with bone marrow harvest; n = 64); the most common in both groups was hip pain (12% [four of 34] versus 23% [seven of 30]) (Table 5).

Treatment-related adverse events related to bone marrow or sham aspiration were reported by 15% (five of 34) of patients in the study group (hip pain, impaired healing, muscle injury, procedural pain, and bone operation) and 7% (two of 30) of patients in the control group (hip pain and injection-site pain) (extended safety set) (Table 5). In the study group, all events except for impaired healing and muscle injury were reported within 1 week of osteoblastic cell transplantation. All events were reported to be mild or moderate in intensity, and all resolved. Only the case of procedural pain was reported as a serious event (see above).

Adverse events that led to withdrawal from the study were reported by 8% (two of 25) of patients in the study group (hip pain) and 3% (one of 29) of patients in the control group (subchondral collapse of the left hip). None of these events were related to the study treatment (Supplemental Digital Content 14; <http://links.lww.com/CORR/B61>).

Vital signs (blood pressure, body temperature, respiratory rate, and heart rate) remained stable in both groups throughout the follow-up period (Supplemental Digital Content 15; <http://links.lww.com/CORR/B62>). There were no clinically relevant changes in hematology and biochemistry laboratory results and physical parameters in either group (Supplemental Digital Content 16; <http://links.lww.com/CORR/B63>).

Discussion

No uniform treatment algorithm exists to treat patients with precollapse ONFH. Although core decompression is the most common procedure to treat these patients, a considerable proportion of patients still undergo THA after core decompression [2, 21, 36, 46]. Thus, it is imperative to seek a more-effective treatment. Several studies have suggested that core decompression combined with cell-based therapies has long-term benefits in patients with early-stage osteonecrosis [7, 12, 24, 30], but robust evidence is lacking. We aimed to evaluate whether autologous osteoblastic cells could improve the results of core decompression in patients with nontraumatic early-stage ONFH. We found no advantage to adding autologous osteoblastic cells to core decompression for patients with early-stage ONFH. Because no clinically meaningful treatment effects associated with bone marrow cell transplantation could be detected, currently, we cannot recommend the combination of this treatment with core decompression unless other well-designed studies can provide evidence of such effects in these patients. Different approaches in which core decompression is combined with other biological treatments should be investigated in the future to improve pain and function and preserve the native femoral head in patients with early-stage ONFH.

Limitations

The main limitation of this study is the small number of included patients, owing to challenging recruitment and many screening failures. This small number of patients did not allow for an assessment of treatment safety, which requires larger populations of patients [18]. In addition, because the study was terminated early, the secondary study endpoints of time to THA and long-term efficacy of the treatment were not assessed. However, the preplanned interim efficacy analysis at 12 months showed that even with a greater number of

patients, the probability of reaching a statistically significant difference between the study and the control groups at 24 months was very low.

Another limitation is the short follow-up of only 2 years, although at that time, we observed that the disease's evolution had plateaued. Additionally, subgroup analyses based on comorbidities associated with ONFH were not performed because of the low number of patients in each group. Finally, the study population included both men and women, but we did not analyze data by gender, which is a potential limitation. Indeed, ONFH predominately affects male patients, which could be related to unknown sex-based factors. Two recent studies assessed the potential association between sex and the outcomes after treatment for ONFH [27, 38]. In a systematic review of 88 studies, women were shown to have a longer time to THA and reduced rate of THA compared with men [27]. However, another prospective study showed gender did not impact the outcome of advanced core decompression [38]. Thus, further studies are needed to assess the impact of gender on the outcomes of treatment for ONFH.

Treatment Efficacy

Our study could not show that the adjunction of autologous osteoblastic cells enhanced the results of core decompression in patients with early-stage ONFH. Although we observed no differences in treatment and radiologic and clinical responses between the study and control groups, in both groups together, 65% of patients treated with core decompression with or without the addition of osteoblastic cells had a good treatment response at 2 years. This was better than the initially assumed proportions of treatment responders of 63% for patients in the study group and 30% for the control group (see Statistical Analysis subsection). We believe that core decompression remains a valuable treatment to preserve the hip in patients with early-stage ONFH. However, to improve the efficacy of this treatment, and considering that in this study cell therapy seemed to be inefficient, future research could focus on other biological therapies (such as growth factor hyperexpression or gene transfer associated with cell therapy).

In contrast to our findings, studies have suggested that core decompression combined with cell-based therapies has benefits in patients with early-stage ON [7, 12, 24, 30]. In a randomized, unblinded study, there were fewer patients with early-stage ONFH whose disease progressed to ARCO fracture stages after core decompression with bone marrow mesenchymal stem cell implantation than after core decompression alone 5 years after the procedure [48]. Recent reviews and meta-analyses have suggested that core decompression combined with stem cell transplantation was more efficacious than core decompression alone in

relieving pain and delaying ONFH collapse [24, 42]. However, the challenges of cell-based therapies for ONFH include defining the number of cells, standardizing procedures, and conducting clinical trials with the most rigorous methods to avoid any confounding factors in a disease that has various and spontaneous outcomes.

The fact that we observed high proportions of treatment responders in both study groups, despite selecting patients with ONFH at risk of collapse or subchondral fracture, could be associated with the homogeneous study population resulting from the use of a comprehensive radiologic assessment. We used CT to detect subchondral fractures at the time of inclusion; several authors have demonstrated the superiority of CT over MRI to detect fractures [23, 33, 39]. Previous studies might have included patients with ONFH who had an impending fracture because they did not use CT to screen for fractures. However, to the best of our knowledge, the effect of cell injection in this setting has never been addressed. It is also possible that core decompression is already an effective treatment on its own, especially because the core decompression technique has largely improved in recent years, with a higher success rate than observed before [3, 34]. Better and more homogeneous imaging quality could have facilitated surgical planning for a more-efficient core decompression procedure. Furthermore, the etiology of ONFH is complex, inconsistent, and incompletely understood, with key specific pathologic processes still to be elucidated, and the repair process may differ among ONFH caused by different etiologies [44]. This, together with the fact that in many patients, the etiology remains unknown, may be an underlying reason for the lack of observed differences in outcomes between the study groups. The inherent cell inefficacy or inaccurate cell quantity in the target area could have also contributed to the lack of an observed added value of osteoblastic cells to core decompression. These considerations are common when autologous material is used in patients at risk of femoral head collapse. This lack of consistency in the quality of autologous osteoblastic cells has also been observed in other treatments in which stem cells are implanted during core decompression and could be linked to factors such as patient age, associated comorbidities, and the etiology of ON [11, 14, 28, 41]. Among these factors, older age has been shown to be associated with a decreased number of mesenchymal stem cells isolated from a donor and their ability to proliferate [4, 19, 24]. However, in our study, patients were relatively young (mean age: 46 years); therefore, it is unlikely they had lower-quality cells because of aging. Furthermore, sufficient cell count (determined by flow cytometry) and cell viability and potency were thoroughly evaluated before implantation. In addition, patients who were randomized to the study group did not receive treatment when the quality of their autologous cells was inadequate. A

previous study with autologous osteoblastic cells implanted during core decompression treatment using a dose of 20×10^6 osteoblastic cells did not yield better results than injecting a bone marrow aspirate concentrate and suggested further research should be done to elucidate whether higher doses might yield better results [11].

Adverse Events

In this study, we did not observe any serious adverse events related to treatment, and nonserious ones were rare in the study and the control groups (4% versus 14%). More patients from the study group than from the control group reported adverse events related to bone marrow (sham) extraction (15% versus 7%), possibly because patients in the control group did not experience bone penetration during the sham procedure. Nevertheless, only one patient reported severe hip pain after bone marrow extraction, while all other adverse events related to this procedure were not severe and resolved. Previous work using the same procedure for culturing cells has shown through karyotype analyses that potential chromosomal abnormalities in osteoblastic cells are uncommon [11]. However, in our study, even if tumor development was not observed, 2 years of follow-up is too short to assess the procedure's safety. A larger number of patients with longer follow-up is needed to confirm the absence of a neoplastic risk.

Conclusion

This double-blind, randomized study did not show any advantage in the use of autologous osteoblastic cells to improve the results of core decompression in patients with early-stage ONFH in terms of pain relief, radiologic progression to fracture ($\geq$ ARCO Stage III), or conversion to THA. There were no serious adverse events related to treatment, and nonserious events were rare. Considering the inefficacy of autologous osteoblastic cells, the high cost of the procedure, and the potential risk associated with cell expansion cultures, we do not recommend combining osteoblastic cells with core decompression unless other well-designed studies can provide evidence of such effects in these patients. Other biologic alternatives should be investigated to improve the results of core decompression.

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