Treatment of Osteonecrosis of the Femoral Head with Implantation of Autologous Bone-Marrow Cells

A Pilot Study

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Background: Aseptic nontraumatic osteonecrosis of the femoral head is a disorder that can lead to femoral head collapse and the need for total hip replacement. Since osteonecrosis may be a disease of mesenchymal cells or bone cells, the possibility has been raised that bone marrow containing osteogenic precursors implanted into a necrotic lesion of the femoral head may be of benefit in the treatment of this condition. For this reason, we studied the implantation of autologous bone-marrow mononuclear cells in a necrotic lesion of the femoral head to determine the effect on the clinical symptoms and the stage and volume of osteonecrosis.

Methods: We studied thirteen patients (eighteen hips) with stage-I or II osteonecrosis of the femoral head, according to the system of the Association Research Circulation Osseous. The hips were allocated to a program of either core decompression (the control group) or core decompression and implantation of autologous bone-marrow mononuclear cells (the bone-marrow-graft group). Both patients and assessors were blind with respect to treatment-group assignment. The primary outcomes studied were safety, clinical symptoms, and disease progression.

Results: After twenty-four months, there was a significant reduction in pain (p = 0.021) and in joint symptoms measured with the Lequesne index (p = 0.001) and the WOMAC index (p = 0.013) within the bone-marrow-graft group. At twenty-four months, five of the eight hips in the control group had deteriorated to stage III, whereas only one of the ten hips in the bone-marrow-graft group had progressed to this stage. Survival analysis showed a significant difference in the time to collapse between the two groups (p = 0.016). Implantation of bone-marrow mononuclear cells was associated with only minor side effects.

Conclusions: Implantation of autologous bone-marrow mononuclear cells appears to be a safe and effective treatment for early stages of osteonecrosis of the femoral head. Although the findings of this study are promising, their interpretation is limited because of the small number of patients and the short duration of follow-up. Further study is needed to confirm the results.

Level of Evidence: Therapeutic study, Level II-1 (prospective cohort study). See Instructions to Authors for a complete description of levels of evidence.

Aseptic nontraumatic osteonecrosis is a painful disorder of the hip that often leads, in its final stage, to femoral head collapse, osteoarthritis, and the need for total hip replacement. Glucocorticoid use and alcohol abuse are among the most widely recognized risk factors for osteonecrosis in white individuals. Core decompression of the hip is the most widespread procedure used to treat early stages of osteonecrosis of the femoral head. Notwithstanding the fact that this procedure has been used for more than three decades, its efficacy remains controversial. Accordingly, a more pathophysi-
A logical approach to the treatment of osteonecrosis may be more appropriate. Different pathophysiological mechanisms have been postulated for this disease, including fat emboli, microvascular tamponade of the blood vessels of the femoral head by marrow fat, retrograde embolization of the marrow fat, and microfracture of trabecular bone. The levels of activity and the number of mesenchymal stem cells in both the hematopoietic and the stromal compartments of the bone marrow have been shown to be depressed in patients with osteonecrosis of the femoral head, suggesting that this might be a disease of bone cells and/or mesenchymal cells. The capacity of osteoblastic cells to replicate is decreased in the proximal part of the femur of patients with osteonecrosis of the femoral head. This finding raised the possibility that bone marrow containing stromal cells, which have many of the characteristics of the stem cells for mesenchymal tissues including bone, could be implanted into a necrotic lesion of the femoral head. Moreover, Hernigou et al. reported the case of a patient who had been treated successfully with autologous bone-marrow implantation for osteonecrosis of the humeral head, secondary to sickle-cell disease. On the basis of this experience, we began a two-year prospective, controlled, double-blind pilot study on the effect of implantation of autologous bone-marrow mononuclear cells into the necrotic lesion in femoral heads with early osteonecrosis.

**Materials and Methods**

**Patients**

Patients were considered eligible for the study if they had stage-I or II osteonecrosis of the femoral head according to the system of the Association Research Circulation Osseous (ARCO). According to this system, normal radiographic findings in the femoral head were classified as ARCO stage-I osteonecrosis; trabecular bone remodeling within the femoral head, as stage II; and subchondral collapse of the femoral head, as stage III. We excluded patients with evidence of a malignant disorder during the past five years. The study was approved by the ethical committee of the hospital, and informed consent was obtained from the patients. Osteonecrosis was diagnosed with magnetic resonance imaging. The primary outcomes that were assessed were safety, clinical symptoms, and disease progression. Clinical symptoms included pain and other joint symptoms. Disease progression included an analysis of the stage of osteonecrosis and the volume of the osteonecrotic lesion at the time of the final follow-up. Since there were no published data on this particular procedure, as far as we know, we could not predetermine the number of hips that would be needed for adequate power in this study. Accordingly, we carried out this pilot study. Seventeen patients were recruited. Four patients were excluded, and thirteen patients (six women and seven men) were able to complete the study. There were no missing data. Demographic data are listed in Table I. At baseline, the stages of osteonecrosis, the age of the patients, the clinical symptoms, and the volume of osteonecrosis for the two groups were not found to be significantly different, with the numbers available.

Five patients had bilateral involvement. Two hips had stage-I osteonecrosis, and sixteen hips had stage-II osteonecrosis. Ten patients (fourteen hips) had osteonecrosis as a result of corticosteroid therapy, and one patient (two hips) had alcohol-induced osteonecrosis. For one patient (two hips), no etiological factor was determined. All patients were symptomatic. The eighteen hips were allocated to treatment with either a core decompression (the control group) or to core decompression and implantation of autologous bone-marrow mononuclear cells (the bone-marrow-graft group). All patients

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**TABLE I Demographic Data and Baseline Characteristics of the Hips**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Control Group</th>
<th>Bone-Marrow-Graft Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of hips</td>
<td>8</td>
<td>10</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>48.8 ± 11.2</td>
<td>40.9 ± 9.8</td>
</tr>
<tr>
<td>Time to diagnosis (mo)</td>
<td>4.6 ± 0.6</td>
<td>5.2 ± 0.9</td>
</tr>
<tr>
<td>Etiology of osteonecrosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Corticosteroid use</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>Alcohol abuse</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Idiopathic</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Visual analog pain scale (mm)</td>
<td>34.6 ± 10.1</td>
<td>37.8 ± 8.4</td>
</tr>
<tr>
<td>Lequesne index</td>
<td>5.4 ± 1.5</td>
<td>7.7 ± 1.5</td>
</tr>
<tr>
<td>WOMAC score</td>
<td>21 ± 5</td>
<td>30 ± 5</td>
</tr>
<tr>
<td>ARCO stage I</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>ARCO stage II</td>
<td>7</td>
<td>9</td>
</tr>
<tr>
<td>Volume of osteonecrosis/volume of femoral head (%)</td>
<td>16.7 ± 4.6</td>
<td>15.6 ± 1.5</td>
</tr>
</tbody>
</table>

*WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index, and ARCO = Association Research Circulation Osseous. †The values are given as the mean and the standard error of the mean.
were blind to the treatment assignment. The hips were not randomized. The surgeon performed both procedures (bone-marrow implantation or a core decompression) on an alternating basis. For patients with bilateral involvement, the surgeon chose which hip to treat first. The first hip to treat was alternately the right and then the left hip. To control for bias, the surgeon never examined the patients before or after the procedure and was the only person to know the group assignment. For ethical reasons, the patient was informed specifically of this procedure and knew that the surgeon could be called in case of complications or side effects. Investigators who assessed the outcomes were blind to group assignment. Recruitment began in January 1999, and all patients were followed for twenty-four months.

Core Decompression
With the patient under general anesthesia, a 5-mm incision was made through the skin and the fascia at the level of the greater trochanter. A 3-mm trephine (inner diameter) (Collin, Paris, France) was used as described by Hauzeur et al.\textsuperscript{14,15}. The trephine was introduced manually under fluoroscopic control through the greater trochanter into the necrotic lesion. The direction of the trephine was adjusted in the intertrochanteric region so that it was pointing toward the necrotic area. The tip of the trephine was placed at a distance of 2 to 3 mm from the articular cartilage (Fig. 1). No other areas of the necrotic lesion were penetrated with the trephine.

Bone-Marrow Grafting
The bone-marrow harvesting was performed during the same operative session as the core decompression. About 400 mL of marrow was obtained from the anterior iliac crest (see Appendix). Mononuclear cells were sorted on a Spectra cell separator (777006-300; Cobe, Lakewood, Colorado) and concentrated to a mean final volume (and standard error of the mean) of 51 ± 1.8 mL, which was injected through the trephine.
phine that was placed into the necrotic zone\textsuperscript{14}. The mean number of leukocytes injected was $2.0 \pm 0.3 \times 10^9$, including $1.0\% \pm 0.2\%$ of CD34$^+$ cells, which are precursors of hematopoietic cells. Fibroblast colony-forming units were used as an indicator of stromal cell activity\textsuperscript{9}. The mean number of fibroblast colony-forming units was $92 \pm 9/10^7$ cells. The sorted bone-marrow mononuclear cells contained lymphocytoid cells (mean, $29\% \pm 2.2\%$), monocytoid cells ($4\% \pm 1\%$), and myeloid cells ($6\% \pm 1.3\%$).

**Clinical Evaluation**

Patients were assessed preoperatively and at three, six, twelve, and twenty-four months postoperatively. Pain was measured with use of a visual analog scale\textsuperscript{17}. The severity of hip disease was gauged with use of the algofunctional index of Lequesne et al.\textsuperscript{18}. Symptoms of osteonecrosis were assessed with the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)\textsuperscript{19}.

At each visit, patients were assessed for possible side effects of treatment.

**Radiographic Evaluation**

Anteroposterior and frog-leg lateral radiographs and magnetic resonance images of the affected hip were made at the time of each clinical assessment. Radiographic progression of the osteonecrosis was measured according to the ARCO staging system\textsuperscript{12}. All radiographs were analyzed by a single reader who was unaware of treatment assignments. The measurements of the magnetic resonance images were prepared on 3-mm coronal T1-weighted scans with use of a separate computer workstation (Easy Vision; Philips, Best, The Netherlands). The contours of the necrotic lesion and the femoral head were drawn on each slice. The volume of the femoral head and the osteonecrotic zone was then calculated by the computer workstation. The relative volume of the necrotic lesion was calculated as a percentage of the entire femoral head\textsuperscript{20}. To evaluate

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**Fig. 3**

Survivorship curves for the bone-marrow-graft group (solid line) and the control group (dashed line), with the collapse of the femoral head (ARCO stage III) as the end point. Kaplan-Meier survivorship analysis showed a significant difference between the two groups with respect to the distributions of the time to collapse at twelve months (log-rank test, $p = 0.038$) and twenty-four months (log-rank test, $p = 0.016$).

**Fig. 4**

A comparison of the bone-marrow-graft group (solid line) and the control group (dashed line) with respect to the evolution of the volume of the necrotic lesion over time. The results are shown as the mean and the standard error of the mean. One asterisk ($p < 0.05$) and two asterisks ($p < 0.01$) indicate a significant difference compared with baseline.
the reliability of this method, the magnetic resonance images were analyzed by two different observers, each unaware of treatment assignments. The first observer took two sets of measurements from each magnetic resonance image of the hip, and the second observer took one. This process resulted in 270 separate determinations.

Statistical Analysis
Continuous variables are described as the mean and the standard error of the mean.

We assessed the change over time with respect to the visual analog scale, the Lequesne index, the WOMAC score, and the volume of the necrotic lesion in both groups. Nonparametric Friedman tests were used. These tests were followed by the use of Wilcoxon paired samples in order to compare the baseline data with the values obtained at three, six, twelve, and twenty-four months. The reliability of the magnetic resonance imaging measurements was calculated with use of correlation coefficients of reliability\textsuperscript{21}. Intraobserver reliability was estimated with use of the readings of the first observer. Interobserver reliability was estimated by taking the first reading of the first observer and the unique reading of the second one. A Kaplan-Meier survivorship analysis was used to compare the progression to subchondral fracture (stage III). The rates of survival of the femoral head for the two treatment groups, that is, the duration between the time of enrollment in the study and the end point (collapse of the femoral head), were compared with the log-rank test. The rates of survival within the subgroups of patients who had bilateral osteonecrosis were also compared. A Cox regression model was used with the rate

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**Fig. 5**
Coronal T1-weighted magnetic resonance imaging scans of two hips showing a reduction in the volume of osteonecrosis (arrow) after bone-marrow implantation (A) and an increase in the volume of osteonecrosis (arrow) in the hip of a control subject after two years (B).
of survival as a dependent variable and with the group and the patient as explained variables. SPSS statistical software (version 11.0; SPSS, Chicago, Illinois) was used.

Results

Overall, a significant decrease in the level of pain was detected in the bone-marrow-graft group after twenty-four months (p = 0.021). The mean scores on the visual analog scale decreased from 37.8 ± 8.4 mm at baseline to 15.1 ± 7.3 mm at three months (p = 0.013), 18.5 ± 6.2 mm at six months (p = 0.017), 23.4 ± 6.7 mm at twelve months (p = 0.066), and 16.3 ± 6.8 mm at twenty-four months (p = 0.017) for the bone-marrow-graft group (Fig. 2). No significant reduction in pain (measured with a visual analog scale) was found in the control group after twenty-four months (p = 0.646), with the numbers available. Overall, patients treated with bone-marrow implantation also demonstrated a marked decrease in joint symptoms after twenty-four months, according to the scores on the Lequesne index (p = 0.001) and the WOMAC index (p = 0.013). In the bone-marrow-graft group, the Lequesne index decreased from a mean of 7.7 ± 1.5 at baseline to 3.6 ± 1.3 at three months (p = 0.011), 3.0 ± 1.1 at six months (p = 0.007), 2.6 ± 1.1 at twelve months (p = 0.008), and 2.2 ± 1 at twenty-four months (p = 0.012) (Fig. 2). In addition, the mean WOMAC score fell from 30 ± 5 at baseline to 13 ± 6 at three months (p = 0.011), 18 ± 7 at six months (p = 0.059), 12 ± 5 at twelve months (p = 0.009), and 12 ± 5 at twenty-four months (p = 0.013) in the bone-marrow-graft group. With the numbers available, no significant decrease in the joint symptoms was detected, according to the scores on the Lequesne index (p = 0.609) and the WOMAC index (p = 0.142), for the control subjects at twenty-four months.

At twenty-four months, five of the eight hips in the control group had deteriorated to stage III, whereas only one of the hips in the bone-marrow-graft group had progressed to this stage. Survival analysis showed a significant difference in the time to collapse between the two groups at twelve months (log-rank test, p = 0.038) and twenty-four months (log-rank test; p = 0.016) (Fig. 3).

Two patients in the control group underwent unilateral total hip replacement. No total hip replacement had been performed in the bone-marrow-graft group at twenty-four months.

Overall, the ratio of the volume of the necrotic lesion to the whole femoral head was 0.959 when measured by one observer, whereas it was 0.776 when measured by two different observers21. These high levels of correlation suggest that the method described was reliable enough to be clinically useful.

Neither bone-marrow grafting nor core decompression caused major side effects. Two patients complained of pain at the site of the bone-marrow aspiration. In one patient, the bacteriological culture of the bone marrow showed coagulase-negative staphylococci. The patient was treated with antibiotics, and no clinical evidence of infection developed. Another patient presented with a hematoma at the site of the core decompression that resolved spontaneously.

Discussion

Our study shows that implantation of bone-marrow mononuclear cells in the osteonecrotic zone appears to be an effective treatment for early stages of osteonecrosis of the femoral head. Implantation of bone-marrow cells decreased the pain and other joint symptoms caused by the osteonecrosis and delayed the progression of the disease to the point of subchondral fracture (stage III) during the twenty-four-month follow-up period.

Many studies have suggested that the likely outcome of osteonecrosis of the femoral head (and, more particularly, the evolution to collapse) is influenced by the size of the lesion, the extent to which the weight-bearing portion of the femoral head is involved22, the stage of the osteonecrosis, and the cause of the osteonecrosis23. However, the most important factor in predicting the outcome of stage-I or II osteonecrosis of the hip is probably the size of the necrotic lesion. Steinberg et al.24 reported that four of thirteen hips that had core decompression and bone-grafting for the treatment of lesions that involved between 15% and 30% of the femoral head required total hip replacement. In contrast, only one of fourteen hips with lesions that involved <15% of the femoral head required replacement. In our study, no significant difference was detected between the control group and the bone-marrow-graft group with respect to the volume of osteonecrosis preoperatively. Therefore, we believe that the patients were similar with regard to the prognosis of the osteonecrosis. Furthermore, the method used to determine the lesion size (magnetic resonance imaging) provides an accurate measure of the volume of both the necrotic segment and the femoral head, a finding confirmed by substantial degrees of intraobserver and interobserver reproducibility.

The progression of the disease was significantly different between the two groups as only one of the ten hips in the bone-marrow-graft group collapsed. This finding is markedly better than that in another series on the natural history of osteonecrosis in which forty-six of seventy hips progressed to stage III25. As far as we know, there are no data on the effect of core decompression with use of a 3-mm trephine on the evolution of osteonecrosis. Conversely, core decompression of the hip with use of an 8-mm trephine is still the most common procedure used to treat the early stages of the disease. Nevertheless, there remains some controversy about its ability to in-
fluence the outcome of osteonecrosis. Mont et al. assessed forty-two studies in which a total of 1206 hips were treated with core decompression and 819 had various nonoperative interventions. Three hundred and forty-five of the 466 hips treated prior to collapse resolved satisfactorily following core decompression, and 182 of the 819 hips that had nonoperative interventions had a satisfactory result. Since we used a 3-mm trephine, our results need to be compared with the results obtained for core decompression with a larger trephine.

A minimum follow-up period of twenty-four months was chosen because collapse of the femoral head generally occurs over this span of time. It also occurs with greater frequency in the first twelve months following the initial diagnosis. Although the findings of this study are promising, their interpretation is limited by the constraints imposed by the relatively small number of patients and the short duration of follow-up.

The bone marrow was injected through the trephine that was placed into the necrotic zone. Although some of the bone-marrow cells might have leaked through the trephine or into the circulation of the proximal aspect of the femur, the greatest part of the bone marrow remained in the area of osteonecrosis or in the femoral head as shown by radionuclide labeling, which was performed in two patients. So far we have been unable to define, using imaging techniques, the exact location of the bone marrow after the injection. Larger trials and the use of other techniques are needed to confirm and to fully understand our results.

Recent advances in our understanding of the pathophysiology of osteonecrosis suggest that a decrease in the mesenchymal stem-cell pool of the proximal aspect of the femur might not provide enough osteoblasts to meet the needs of bone-remodeling in the early stage of the disease. An insufficiency of osteogenic cells could explain the inadequate repair mechanism that, it is postulated, leads to femoral head collapse. The effectiveness of bone-marrow mononuclear cells may be related to the availability of stem cells endowed with osteogenic properties, arising from an increase in the supply of such cells to the femoral head through bone-marrow implantation. Indeed, in the very early stages of osteonecrosis, providing sufficient repair capacity through the implantation of osteogenic cells could make these lesions reversible.

In our study, the ratio of the volume of the necrotic lesion decreased by a mean of 35% in the bone-marrow-graft group, whereas it increased by a mean of 23% in the control group. This finding suggests that necrotic lesions might be reversible to some extent. Another possible explanation for the therapeutic effect of bone-marrow implantation is that injected marrow stromal cells secrete angiogenic cytokines resulting in increased angiogenesis and subsequent improvement in osteogenesis. One study has suggested that the efficacy of such implantation was due to a supply of endothelial progenitor cells included in the CD34+ fraction as well as to multiple angiogenic factors (vascular endothelial growth factors, basic fibroblast growth factor, and angiopoietin-1) released from the CD34+ fractions.

In summary, we have shown the efficacy and apparent safety of the implantation of bone-marrow mononuclear cells in the early stages of osteonecrosis of the femoral head in a small number of patients. This promising new approach for the treatment of osteonecrosis could benefit from the recent advances made in the field of stem-cell biology, including the use of subpopulations of progenitors with greater therapeutic potential.

Appendix

A description of the details of the bone-marrow harvest and grafting procedure is available with the electronic versions of this article, on our web site at www.jbjs.org (go to the article citation and click on “Supplementary Material”) and on our quarterly CD-ROM (call our subscription department, at 781-449-9780, to order the CD-ROM).

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