THERAPY WITH STEM CELLS IN THE TREATMENT OF
ISCHEMIC NECROSIS IN FEMORAL HEAD
Osteonecrosis repair with stem cells: 30 years of
experience with bone marrow concentration.

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> 200 patients with
osteonecroses

treated / year

PLAN

• Rationale of the technique
• Technique
• Clinical results
• Repair of osteonecrosis
• How many cells are necessary ?
• Other techniques of graft improvement
  Work in progress – Tissue Engineering
• Conclusion and indications

Autologous Bone Marrow Grafting
before Collapse

At its first stages, before collapse, osteonecrosis is characterized
by presence of dead bone and absence of mechanical failure.
Presence of a vascular
demarcating line

So, injection of osteogenic cells
in the dead area should improve
the repair process

There is a decrease of MSCs in the femoral
head of patient with osteonecrosis

- Hernigou P, Decrease in the mesenchymal stem-cell pool in osteonecrosis.
- Calder JD, The extent of osteocyte death in the proximal femur of patients
- Gangji V, Abnormalities in the replicative capacity of osteoblastic cells in
  osteonecrosis of the femoral head. J Rheumatol
- Suh KT, Kim SW, Roh HL, Youn MS, Jung JS Decreased osteogenic
- Chang JK, Ho ML, Yeh CH, Chen CH, Wang GJ Osteogenic gene
  expression decreases in stromal cells of patients with osteonecrosis. Clin

Autologous Concentrated
Bone Marrow Grafting
1986 – 2017 (30 years)

> 3000 hips

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Bone marrow can be collected from either the anterior or posterior part of the iliac crest. Supine position the patient permits the access to the anterior iliac crest (IC). The trocard should remain well within the tables of the crest.

**Bone Marrow Aspiration**
Red marrow of the Iliac Crest
- After deep insertion into spongy bone, of a beveled needle (6 to 8 cm in length and 1.5 mm in internal diameter), the marrow is aspirated into a 10-mL plastic syringe.

**Concentration of Bone Marrow**
After a 5 minutes centrifugation at 1200 g:
- The centrifugation forces the polymuclear cells (with the heavier nuclei) to be in the periphery where they can be removed.
- The lighter anuclear red cells are found in the center and can also be removed.
- Only mononuclear cells (with Stem Cells) are kept and useful for grafting.

**MSCs obtained by aspiration.**

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Qualitative Repair on MRI: Total Resolution

Resolution of osteonecrosis may be observed at stage I
- These osteonecroses had a normal fat intensity area with a marginal band-like pattern.
- During the resolution of disease, intralesional area with low intensity on T1 images were observed before a return to a normal fat intensity area with disappearance of the marginal band-like pattern.
- Time for resolution may be as long as 10 years.

Qualitative Repair on MRI: Sub-total Resolution
Stage I:
Good functional result and spherical head without collapse
But a small intralesional area with low intensity on T1 remained on the MRI at the most recent follow-up at 22 years.

Qualitative Repair: Condensation on radiograph and CT-scan
Stage II:
Good functional result and spherical head without collapse at the most recent follow-up at 20 years.

Anatomical evaluation of revascularization
Quantitative evaluation: microangiography
Stage II osteonecrosis treated without stem cells therapy
Injection of the circonflex artery on anatomical specimen after section of the neck during total hip arthroplasty:
- No revascularization of the necrotic area

Anatomical evaluation of revascularization
Qualitative evaluation: macroscopic aspect
Same patient with bilateral osteonecrosis
Core decompression alone
Autologous bone marrow injection

Anatomical evaluation of revascularization
Stage II osteonecrosis treated with MSCs
Microangiography shows revascularization of the necrotic area.
3-D microangiography of the femoral head

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**Conditions for corticosteroids**

- Lupus erythematosus, uveitis, eosinophilic granuloma, multiple sclerosis, Crohn’s disease, pemphigus vulgaris, nephrotic syndrome, liver transplantation, renal transplantation, aplastic anaemia, cardiac transplantation….

  - 65 patients cumulative glucocorticoid dose > 4g
  - 35 patients glucocorticoid use between 2g and 4g
  - 25 patients received < 2g.

**Hips**

- Stage I, 138 hips (69 patients);
- Stage II 112 hips (56 patients).
- Same trocar; same technique
- Core decompression one one side
- BM injection same day: The average total number of MSCs (counted as CFU-F) injected in hip was 90,000 ± 25,000 cells (range 45,000 to 180,000 cells).
- Follow-up: 20 to 30 years; mean 25 years

**Bone marrow implantation decreased the number of hips that progressed to collapse:**

- 250 hips included in the study (125x2)
- 35 hips had collapsed at the most recent follow-up after bone marrow grafting 28%
- 90 after core decompression 72%

  - (28%, 35 among 125 versus 72%, 90 among 125; odds ratio 0.1512, 95% confidence interval [CI] 0.0871 - 0.2627; P < 0.0001).
Bone marrow implantation decreased the need for primary total hip replacement.

- 95 THA (76%) in the CD group
- 30 THA (24%) with bone marrow graft (p < 0.0001).

Bone marrow decreased the need for revision and re-revision of total hip replacement

- CD: 45 of 95 THA required one revision (second THA) and 5 of these 45 hips a re-re-revision (at 18, 22, 26, 29 years FU after core decompression).
- BM: 2 of 30 THA had a revision.

Bone marrow injection improved the repair process on MRI

- There was a significant difference (p<0.0001) in the number of hips with repair between hips with core decompression alone and hips with BM.
- For hips with repair, there was a significant difference in the volume of repair between hips with core decompression and hips with bone marrow injection.
- For hips treated with BM injection, volume decrease from 45% to 17%, as percentage of the volume of the femoral head.
- With CD decrease moved from 35.8% to 27.6%.

Discussion

- Better results for stage I and II
- Better results for small volume
- This rough estimate of effect size and effect stage in the same patient in a series with the cause of ON is the same may explain various odds for conversion to THA in the literature when the cell therapy is compared to the core decompression in different patients with different causes of ON, and when volume and stage of ON are not matched.

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NORMAL FEMORAL HEAD

Homma Y, Kaneko K, Hernigou Int Orthop. 2013

- Average 700±264 MSCs per cm³ with average volume of 50 cm³.
- 35 000 MSCs may be considered as a useful approximation of the number of MSCs present in a femoral head.

This number may be considered as the target number to load in a femoral head with osteonecrosis to have the same number of MSCs than in a normal femoral head.

Femoral Head with Osteonecrosis

- Necrosis area: no MSCs
- Outside: decreased to 200 MSCs per cm³

Total < 3000 MSCs
Theoretical Assessment of MSC Levels in Treating ONFH

- A normal 50 cm³ femoral head contains approximately 36,000 MSCs.
- In a 30% Osteonecrosis, 12,000 MSCs are missing in the femoral head.
- Only 30% to 50% of the injected stem cells remain in the femoral head (studied by Hernigou and Gangji).
- That means that it is necessary to inject at least 12,000 x 3 = 36,000 MSCs depending on the volume, cause of osteonecrosis, unilaterality or bilaterality.

Other techniques of graft improvement

Work in progress – Tissue Engineering

CELLS PRODUCTION
- Expansion of the number of Autologous Cells by culture:
  - with or without scaffold
  - +/- growth factors
- Allogenic stem cells grafts
- Genetic Therapy

WAY OF ADMINISTRATION
- Directly in bone with scaffold
- Intra-arterial circumflex injection
- Intravenous injection for multifocal osteonecrosis

Results

- Each side: same volume of concentrated bone marrow and number of cells.
- The average total number of MSCs counted as CFU-F injected in each hip was 110,000 ± 27,000 cells (range 50,000 to 190,000 cells).
- Using computer navigation took:
  - fewer attempts to position the trocar,
  - used less fluoroscopy time,
  - and decreased the radiation exposure.
- Increasing the precision with computer navigation resulted in:
  - less collapse (7 versus 1)
  - and better volume of repair (13.4 versus 8.2 cm³) for hips treated with the computer-assisted technique.

Expansion of the number of Autologous Cells by culture for osteonecrosis (Reborn study)

Allogenic Stem Cells Grafts

**Indication:**
Patients with impossibility to get enough autologous stem cells even after expansion

**Intravenously delivery of allogenic bone marrow-derived stem cells**


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**First Conclusion**

**Autologous concentrate Bone Marrow : safety and efficiency**

- **Efficiency:**
  - A 25 years experience with more than 2000 hip osteonecroses

- **Indications:**
  - Stage I and II
  - Stage III with crescent line or collapse < 2mm

- **Etiologies:**
  - Sickle cell disease; alcohol abuse; corticosteroids, idiopathic...

- **Safety:**
  - Very few complications (per-operative hypotension : 2 cases)
  - No fractures when using a small diameter trocar (4 mm)
  - Patients treated with cell therapy do not have a greater incidence of cancer than the rest of the population*


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**Second Conclusion**

Work is in progress

- **Expansion or allogenic stem cells could be necessary in some indications:**
  - Patients with stem cells deficiency such as post-chemotherapy...
  - Patients with multifocal osteonecrosis (Sickle cell disease)

- **Allogenic grafts are already possible:**
  - but total immunological safety is not proved

- **Expansion is promising but**
  - Still in experimentation
  - Cost is very high as compared with concentration
  - Safety is not proved

THANK YOU FOR YOUR ATTENTION