Regenerative therapies increase survivorship of avascular necrosis of the femoral head: a systematic review and meta-analysis

Luca Andriolo¹ · Giulia Merli² · Carlos Tobar³ · Sante Alessandro Altamura¹ · Elizaveta Kon^{4,5} · Giuseppe Filardo²

Received: 2 August 2017 / Accepted: 18 January 2018 / Published online: 6 February 2018
© SICOT aisbl 2018

Abstract

Purpose The aim of this study was to document the available evidence on the use of regenerative techniques for the treatment of femoral head osteonecrosis (or avascular necrosis of femoral head, AVN) and to understand their benefit compared to core decompression (CD) alone in avoiding failure and the need for total hip replacement (THR).

Methods The search was conducted on three medical electronic databases according to PRISMA guidelines. The studies reporting number and timing of failures were included in a meta-analysis calculating cumulative survivorship with a Kaplan-Mayer curve. Moreover, the results on failures in treatment groups reported in RCT were compared with those documented in control groups, in order to understand the benefit of biological therapies compared to CD for the treatment of AVN.

Results Forty-eight studies were included in this systematic review, reporting results of different types of regenerative techniques: mesenchymal stem cell implantation in the osteonecrotic area, intra-arterial infiltration with mesenchymal stem cells, implantation of bioactive molecules, or platelet-rich plasma. Overall, reported results were good, with a cumulative survivorship of 80% after ten year follow-up, and better results when regenerative treatments were combined to CD compared to CD alone (89.9% vs 70.6%, $p < 0.0001$).

Conclusion Regenerative therapies offer good clinical results for the treatment of AVN. The combination of CD with regenerative techniques provides a significant improvement in terms of survivorship over time compared with CD alone. Further studies are needed to identify the best procedure and the most suitable patients to benefit from regenerative treatments for AVN.

Keywords Hip · Avascular necrosis of femoral head · Osteonecrosis · Regenerative therapies · Biological therapies · Core decompression

Introduction

Osteonecrosis of the femoral head or avascular necrosis (AVN) is a pathological process that most commonly affects

young adults in the third and fourth decades of their life. Its incidence is increasing, and every year, 10,000 to 20,000 new cases are diagnosed in the USA [1].

AVN can follow traumatic or non-traumatic conditions. The cause of atraumatic osteonecrosis of the femoral head is believed to be multifactorial, in some cases associated with both genetic predisposition and exposure to risk factors [2]. These include, but are not limited to, corticosteroid use, alcohol abuse, previous trauma, haemoglobinopathy, Gaucher's disease, and coagulopathies. The onset of AVN may also be idiopathic [3]. Regardless of the specific initiating event, failure of perfusion may occur due to three mechanisms [2]: vascular interruption, vascular occlusion, and extravascular compression. Any of these leads to a decreased blood supply/ischaemia in the femoral head. After a variable period of ischaemia, osteocyte, adipocyte, and haemopoietic marrow necrosis occurs, followed by a sequence of reactions and variable repair attempts [2]. Although remodeling cycle continues

✉ Giulia Merli
giuliamerli85@gmail.com

¹ II Orthopaedic and Traumatologic Clinic, Rizzoli Orthopaedic Institute, Bologna, Italy

² Nano-Biotechnology Laboratory-NaBi, Research and Innovation Technology Department, Bologna, Italy

³ Department of Orthopedics and Traumatology, Avansalud Clinic of Santiago, Santiago, Chile

⁴ Humanitas University Department of Biomedical Sciences, Milan, Italy

⁵ Humanitas Clinical and Research Center, Milan, Italy

in adjacent areas of bone with an intact blood supply and viable cells, bone resorption generally predominates, causing further weakening of subchondral bone, progressive collapse of subchondral trabeculae, and, ultimately, development of osteoarthritis [4].

It is estimated that 5–12% of total hip replacements (THRs) each year are performed to treat this disease [1], but their outcome has been shown to be less satisfactory compared to other indications, primarily due to the limited lifetime and durability of THR in such young patients [4, 5]. As a result, there is an increasing focus on the development of early interventions for AVN, aimed at preserving the native articulation to avoid or at least delay THR [5]. Core decompression (CD) is currently the most widely accepted surgical treatment for early-stage AVN [6]. The rationale of its use is to reduce or decompress the intraosseous pressure in the femoral head, resulting from venous congestion and other pathways, in order to promote vascular invasion and to facilitate regeneration of the necrotic tissue. However, the overall clinical success rate of CD has been shown to be only 63.5%, and the rate for subsequent THR or hip salvage surgery is about 33% [7]. For this reason, its use has been debated [4] and, with the scope of improving CD results, the use of different regenerative techniques has recently been proposed to address early AVN stages.

The aim of this study was to document the available evidence on regenerative techniques in AVN with a systematic review, and to perform a meta-analysis of their results in preserving subchondral bone from collapse compared to CD, thereby avoiding failure and the need for THR.

Materials and methods

A systematic review of the literature was performed on biologic therapies for AVN. The search was conducted on June 23, 2017, using the following parameters on three medical electronic databases (PubMed, Scopus, and the Cochrane Collaboration): ((Stem cells) OR (bone marrow) OR (mesenchymal bone marrow) OR (biological therapies) OR (regenerative therapies)) AND ((femoral head surgery) OR (femoral head decompression) OR (hip decompression)) AND ((osteonecrosis) OR (necrosis) OR (bone marrow oedema) OR (bone marrow pathology)). The guidelines for Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) were used [8]. Screening process and analysis were conducted separately by two independent observers (GM and SAA).

First, the articles were screened by title and abstract. The following inclusion criteria for relevant articles were used during this initial screening: clinical reports of any level of evidence, written in English language, with no time limitation, on biological regenerative therapies used to treat patients

affected by hip AVN. Exclusion criteria were articles written in other languages, preclinical studies, reviews, or clinical studies analyzing non-biological techniques. In the second step, the full texts of the selected articles were screened, with further exclusions according to the previously described criteria. Furthermore, articles not reporting clinical outcome data were excluded. Reference lists from the selected papers were also screened. Relevant data (type of study, type of treatment, no. of patients, age of the patients, disease staging, aetiology, follow-up, results, complications, and failures) were then extracted and collected in a unique database with consensus of the two observers to be analyzed for the purposes of the present manuscript.

The primary aim of this review was to document through a qualitative analysis the different types of biological therapies applied in the clinical practice to treat hip AVN. Secondly, the results of these procedures were further analyzed quantitatively, aiming at understanding their clinical potential in terms of survivorship and THR prevention compared to CD. To this aim, studies reporting number and timing of failures were selected, and the cumulative survivorship was analyzed with a Kaplan-Mayer analysis [9, 10]. Studies were included in the Kaplan-Mayer analysis only if they reported, for every single failure, either the specific time of revision to THR, or at least a failure time in an interval no longer than 2 years. Moreover, the results on failures in treatment groups reported in randomized controlled trials (RCTs) were compared with those documented in control groups, in order to understand the benefit of biological therapies compared to CD for the treatment of AVN.

Results

The database search identified 713 records, and the abstracts were screened and selected according to the inclusion/exclusion criteria. As shown in Fig. 1, a total of 66 full-text articles were assessed for eligibility. Eighteen articles did not fulfill the criteria and were further excluded, leading to a total of 48 studies used for the qualitative analysis (a detailed description of these studies is reported in Table 1). As shown in Fig. 2, two thirds were published in the last four years, showing an increment in the interest on this surgical approach, whereas only 16 articles had been published in the previous 11 years. Overall, the evaluation of evidence level showed eight RCTs, two prospective comparative studies, seven retrospective comparative studies, 28 case series, and three case reports.

The biologic therapies analyzed in the included studies were heterogeneous, often applied in different combinations, mostly associated with the use of classic procedures (like CD or drilling), and sometimes associated bone substitutes (details of the specific procedures applied in each study are reported in

Fig. 1 PRISMA flowchart of the systematic literature review

Table 1). From a biologic point of view, four different types of treatment could be distinguished:

1. Stem cells applied in the osteonecrotic area: bone marrow-derived MSCs, mostly as bone marrow concentrate (BMC) [11–40], more rarely cultured [41–45] or simply as bone marrow aspirates [46, 47], adipose-tissue-derived MSCs [48], or allogeneic human umbilical cord-derived MSCs [49].
2. Intra-arterial injection of stem cells: the types of stem cells used with this approach were peripheral blood MSC mobilized by G-CSF [50], allogeneic human umbilical cord-derived MSCs [51], bone marrow-derived MSCs [52], or the combination of the last two methods [53].
3. Bioactive molecules: recombinant human bone morphogenetic protein: rhBMP-2 [12, 54], rhBMP-7 [47, 55], partially purified human BMP [56], or rhFGF-2 [57].
4. Platelet-rich plasma: either used with bone graft [58], BMC [24], or adipose-tissue derived MSCs and hyaluronic acid [48].

The included studies also involved the use of different bone substitutes: autografts [21, 23, 25, 29, 54, 55, 58] (including also vascularized bone grafts [41–43]), allografts [28], xenografts [47], synthetic bone grafts, and scaffolds [27, 31, 34, 38,

45, 47, 57]. Metal constructs were also applied to reinforce bone architecture [42, 49, 50]. Some studies also combined pharmacological treatments, like intravenous iloprost [11] or oral bisphosphonates [13], hyaluronic acid [48], or physical therapy with low-intensity pulsed ultrasound [14].

These studies reported the results of AVN treatment in 2645 hips of 1988 patients. The populations included in the selected studies were very heterogeneous in terms of age, etiology, and AVN stage. Age presented a wide range: while mean age was around 35–45 years, patients ranged from children and teenagers to seniors. Only two studies analyzed specifically young populations, affected by sickle cell disease in one case [22] and by AVN after femoral neck fractures in the other [12]. Etiology included steroid therapy (847 hips), alcohol (515 hips), sickle cell disease (446 hips), idiopathic (364 hips), trauma (121 hips), chemotherapy (8 hips), smoke (13 hips), immunosuppressive therapy (29 hips), HIV (10 hips), lupus (23 hips), pregnancy (1 hips), Cushing disease (1 hips), Caisson disease (11 hips), hepatitis C (3 hips), or other not specified etiologies (25 hips). AVN stage was evaluated with different systems: Association Research Circulation Osseous (ARCO) classification in 19 articles [11, 12, 15, 16, 19, 27, 29, 33, 35, 38, 39, 42–44, 50, 51, 53, 54], Ficat classification in 14 articles [13, 17, 20, 23–25, 28, 38, 46, 47, 49, 52, 55, 58], Japanese Orthopaedic Association (JOA) classification in 5

Table 1 Detailed description of the 48 studies selected in the systematic review

Author	Level of evidence	Patient/hip treated	Age (years)	Staging	Etiology	Technique	Follow-up	Conclusions	Complications/notes
Pilge et al. Ortho Rev 2016	Level II Prospective comparative study	20/20 Control group: 10 Treatment group: 10	38.4 (15–58)	ARCO 2: 12 ARCO 3: 6 ARCO 4: 2	Steroid: 5 Idiopathic: 8 Smoke: 1	Control group: CD + iloprost iv. Treatment group: CD combined with BMC + iloprost iv.	30.6 months (4–69)	An improvement in clinical scores was shown in treatment group, but not in control group. 2 patients in treatment group and 4 in control group were treated with THR.	No serious adverse reaction to iloprost infusion. 3 patients had flush symptoms and 2 patients complained of a mild headache during infusion.
Chen et al. Molecular Medicine Reports 2016	Level IV Case series	9/9	41.1 (28–51)	ARCO II: 5 ARCO IIIa: 4	Steroid: 6 Alcohol: 2 Idiopathic: 1	Intra-arterial injection of hUC-MSCs	24 months	Intra-arterial infusion of hUC-MSCs promote the repair and regeneration in the condition of bone necrosis.	No specific complication. Injected cells: $5-10 \times 10^6$ cells/ml.
Gao et al. Nature Scientific Report 2016	Level IV Case series	51/51	16.3 (11.4–18.1)	ARCO I: 3 ARCO II: 21 ARCO III: 27	Femoral neck fractures	CD + implantation of BMC and rhBMP-2	6.8 years	The combination of CD + implantation of BMC and rhBMP-2 provided beneficial effects for hips affected by early- to middle-stage osteonecrosis after femoral neck fractures in children and adolescent. 1 patient required THR.	9/51 hips showed radiological collapse of the femoral head or narrowing of the hip joint space.
Gianakos et al. HSS Journal 2016	Level III Retrospective comparative study	49/62 Control group: 40 Treatment group: 22	Control group: 43 Treatment group: 38	Control group: 20 Ficat I: 3 Ficat IIa: 25 Ficat IIb: 1 Treatment group: 8 Ficat I: 1 Ficat IIa: 13 Ficat IIb: 6	Control group: Steroid: 20 Idiopathic: 15 Anticoagulation: 4 Trauma: 1 Treatment group: Steroid: 8 Idiopathic: 12 Anticoagulation: 2	Control group: Bisphosphonate therapy alone Treatment group: Bisphosphonate therapy in combination with CD and BMC	Control: 25.3 months Treatment: 22.7 months	This study demonstrates no significant difference in clinical outcomes between the two treatment groups. Treatment with bisphosphonate + CD + BMC show a similar chance of progressing in AVN compared to hips treated with bisphosphonate alone. 21/40 hips in control group and 5/22 hips in treatment group required a THR.	
Mishima et al. Eur J Orthop Surg Traumatol 2016	Level IV Case series	14/22	40 (20–58)	JOA B: 2 JOA C1: 10 JOA C2: 10	Steroids: 15 hips Trauma: 3 hips Alcohol: 2 hips Idiopathic: 2 hips	CD with BMC and LIPUS	26 months (24–30)	BMC plus LIPUS offer a safe and effective treatment of AVN. Progression of collapse in 8/22 hips, but none required THR.	Injected cells: 2.91×10^7 cells/ml.
Yan et al. Current Orthopedic Practice 2016	Level III Retrospective comparative study	86/86 Control group: 42 Treatment group: 44	Control group: 37.2 Treatment group: 39.6	Control group: 2 ARCO I: 2 ARCO II: 40 Treatment group: 2 ARCO I: 3 ARCO II: 41	Control group: Steroid: 29 Alcohol: 13 Treatment group: Steroid: 28 Alcohol: 16	Control group: CD alone Treatment group: CD + BMC implantation	26.3 months	BMC transplantation in addition to CD relieves articular pain and delay the progression of early AVN. 4 hip in control group and 1 in treatment group underwent THR.	No complications were observed. Injected cells: 3.76×10^7 cells/ml.
Pepke et al. Orthopedic Reviews 2016	Level I Randomized controlled clinical trial	24/25 Control group: 14	Control group: 44.5	ARCO II: 25	Chemotherapy: 2 Immunosuppressive therapy: 4	Control group: CD alone Treatment group: CD + BMC implantation	24 months	No significant benefit from the additional injection of BMC in the short term.	Injected cells: 118.9×10^6 cells/ml.

Table 1 (continued)

Author	Level of evidence	Patient/hip treated	Age (years)	Staging	Etiology	Technique	Follow-up	Conclusions	Complications/notes
Samy et al. Indian J Orthop 2016	Level IV Case series	Treatment group: 11 30/40	Treatment group: 44.3 36.7 (20–48)	Ficat IIb: 16 Ficat IIi: 24	Steroid: 15 Idiopathic: 20 Trauma: 5	Drilling of necrotic area and filled with a composite of bone graft mixed with PRP	41.4 months (36–50)	6/14 in control group and 4/11 in treatment group underwent THR. The use of bone graft mixed with PRP improve the repairable capacity of necrotic area. 4 hips underwent THR. No significant radiologic and clinical differences between outcome of CD plus BMC and CD alone. 10/19 hips in control group and 22/41 in treatment group required a THR.	No complications were observed.
Cruz-Pardos et al. Hip Int 2016	Level III Retrospective comparative study	Control group: 45/60 19 Treatment group: 41	Control group: 36.7 (20–68) Treatment group: 42.6 (23–70)	Control group: Ficat I: 5 Ficat II: 11 Treatment group: Ficat I: 8 Ficat II: 33	Steroid: 6 Alcohol: 5 Idiopathic: 6 Anticoagulation: 1 Other: 1 Treatment group: Steroid: 14 Alcohol: 3 Idiopathic: 12 HIV: 8	Control group: CD alone Treatment group: CD combined with BMC grafting into the core tract	45 months (24–171)		
Kuroda et al. Int Orthop 2015	Level IV Case series	10/10	39.8 (29–53)	JOA Stage I: 1 Stage 2: 9 Type A: 1 Type B: 1 Type C1: 1 Type C2: 7	Steroid: 18 Alcohol: 6 Idiopathic: 7	CD with single local administration of 800 µg of rhGF-2-impregnated gelatin hydrogel	12 months	Stage progression and collapse did not occur in nine cases, with significant improvement of clinical scores by one year postoperatively. Computed tomography confirmed bone regeneration in the femoral heads. Only one case of femoral head collapse requiring THR.	1 adverse event related to surgery (headache due to spinal anesthesia).
Persiani et al. Acta Orthop Belg 2015	Level IV Case series	29/31	34 (26–53)	Steinberg I: 11 Steinberg II: 16 Steinberg III: 2 Steinberg IV: 2	Steroid: 18 Alcohol: 6 Idiopathic: 7	CD + BMC implantation	37 months (23–48 months)	25 hips showed relief of symptoms and resolution of the osteonecrosis at magnetic resonance imaging. The progression of the disease occurred in 6 hips (2 Stage II, 2 Stage III and 2 Stage IV), which required THR. This technique is effective in delaying THR in early stages. This combined treatment provides significant improvements of HHS without failures in the first year of F-up, suggesting that is effective for the treatment of early AVN Progression of the disease only in one case at 18 m F-up.	No complication was observed.
Gao et al. J Nanomater 2015	Level IV Case series	12/12	–	Ficat II: 12	–	Implantation of novel nanoscaled CD rod + umbilical cord MSC	12 months		No complication was observed.
Aoyama et al. Arch Phys Med Rehabil 2015	Level IV Case series	10/10	31.7 (20–48)	JOA IIIA: 6 JOA IIIB: 4	Steroid: 4 Idiopathic: 6	Cultured bone-marrow derived MSC transplantation augmented by vascularized bone grafting	12 months	Cultured bone-marrow derived MSC transplantation in individuals with AVN provides significant improvements on external rotation, extensor and abductor muscle strength, and physical function, without THR.	No serious complication were noted. Intense rehabilitation program.

Table 1 (continued)

Author	Level of evidence	Patient/hip treated	Age (years)	Staging	Etiology	Technique	Follow-up	Conclusions	Complications/notes
Tabatabaee et al. J Arthroplasty 2015	Level I Randomized controlled clinical trial	18/28 Control group: 14 Treatment group: 14	29.08 (18–56) Control group: 26.8 Treatment group: 31	ARCO I: 5 ARCO II: 16 ARCO III: 7	Steroid: 19 Idiopathic: 9	Control group: CD alone Combination treatment group: CD + BMC implantation	24 months	BMC injection with CD could be an effective therapy for the early stages of AVN, with score improvement. No failures and better radiological results compared to control group.	No serious complication were noted in both the clinical groups.
Dalro et al. Stem Cell Res Ther 2015	Level IV Case series	89/89	33 (18–55)	Ficat I: 20 Ficat I: 31 Ficat IIa: 16 Ficat IIb: 22	Sickle Cell Disease	Injection of BMC through a percutaneous approach in the center of the osteonecrotic area	37.3 months (12–60 months)	Injection of BMC provides significant improvement of HHS score in all ONHF stages, as well as reduces pain, ameliorates quality of daily activities, and prevents the progression of the diseases without any conversion to THR.	No complications were observed during or after the treatment. Injected cells: 9.7×10^8 cells. BMC derived from SCD patients maintain the ability of osteogenic differentiation.
Mao et al. J Bone Miner Res 2015	Level I Randomized controlled clinical trial	55/89 Control group: 25/41 Treatment group: 30/48	35.3 (18–65) Control group: 36.1 Treatment group: 34.6	ARCO I: 18 ARCO II: 52 ARCO IIIa: 19	Steroid: 31 Alcohol: 32 Idiopathic: 26	Control group: Biomechanical support to the subchondral bone (porous tantalum rod implantation) Combination treatment group: Biomechanical support + Intra-arterially injection of peripheral blood MSC mobilized by G-CSF	36 months	Combination treatment provides superior results regarding clinical outcome such as pain, function, activity, and motion compared to biomechanical support alone. 3 hips underwent THR in treatment group, compared to 9 in control group. The treatment provides improvements of HHS score in all ONHF stages. THR required in 5/31 joints.	No complication was observed. Injected cells: 2.47×10^8 which contained $1.71 \pm 0.7 \times 10^6$ CD34 ⁺ cells.
Zhao et al. Biomed Res Int 2015	Level IV Case series	24/31	33.21 (23–45)	ARCO I: 4 ARCO II: 19 ARCO IV: 12	Idiopathic: 4 Steroid: 14 Alcohol: 4 Trauma: 2	Cultured bone-marrow derived MSC transplantation associated with porous tantalum rod implantation combined with vascularized iliac grafting	64.4 months (26–78 months)	The treatment provides an overall success of 80%, their HHS had significant improvement and this new method was best for early-stage small lesions. 4 clinical failures, but no THR.	No complication was observed in both treatment groups. Injected cells: 20^6 cells/ml.
Wang et al. Eur Orthop Surg Traumatol 2014	Level IV Case series	15/20	35 (23–58)	ARCO I: 10 ARCO II: 6 ARCO IIIa: 3 ARCO IIIb: 1	Steroid: 4 Alcohol: 4 Idiopathic: 12	BMC mixed with cortical and cancellous bone (harvested from the ipsilateral crest) were impacted into the excavated area	24 months (9–36 months)	The treatment provides an overall success of 80%, their HHS had significant improvement and this new method was best for early-stage small lesions. 4 clinical failures, but no THR.	No complication such as infection, femoral neck fracture were seen during operation and postoperation.
Cai et al. Transplant Proc 2014	Level IV Case series	30/49	41.6 (19–63)	ARCO I: 12 ARCO II: 24 ARCO III: 25	Steroid: 12 Alcohol: 9 Idiopathic: 9	Intra-arterially injection of allogeneic human umbilical cord-derived MSCs and BMC	16.9 months (12–21)	The treatment provide significant therapeutic effects in AVN, without conversions to THR.	No complication was observed.
Sun et al. PLoS One 2014	Level III Retrospective comparative study	42/72 Control group: 39 Treatment group: 33	30.9 (22–54) Control group: p:30.7 Treatment group: 31.1	Control: ARCO I: 6 ARCO II: 18 ARCO IIIa: 19	A majority of the patients had a history of SARS and were treated with high-dose corticosteroids.	Control group: Standard background therapy (impacted bone grafting) Treatment group: Standard background therapy + rhBMP-2	6.1 years (5–7.7 years)	The use of rhBMP-2 could be useful to improve the speed and quality of the bone repair but this study lacks of statistical difference. The survival rate of the femoral head was 71.8% and 81.8% in control	Postoperative complications: 3 ectopic ossification in (2 in bone grafting + rhBMP2 and 1 in bone grafting group); 4 lateral femoral cutaneous nerve lesion (both 2 hips in the 2 groups). Excellent and good results in selected patients (ARCO II).

Table 1 (continued)

Author	Level of evidence	Patient/hip treated	Age (years)	Staging	Etiology	Technique	Follow-up	Conclusions	Complications/notes
Aoyama et al. Tissue Eng Part B Rev 2014	Level IV Case series	10/10	31.7 (20–48)	ARCO IIB: 4 ARCO IIC: 21 ARCO IIIA: 11 ARCO 3A: 6 pt. ARCO 3B: 4 pt. Steinberg 3: 6 Steinberg 4: 4	Steroid: 4 Idiopathic: 6	Cultured bone-marrow derived MSC + vascularized iliac bone graft	24 months	This procedure is safe and no conversion to THR was registered, with clinical improvement and good bone regeneration.	Frequent complications: increase in creatine phosphokinase and C-reactive protein, anemia, hip pain, decrease in albumin and total protein, complications at the wounded area, wound pain, and fever. Injected cells: 1.2×10^8 cells.
Novais et al. J Pediatr Orthop 2014	Level IV Retrospective case series	11/14	12.7 (9.7–18)	Steinberg IB: 1 Steinberg IC: 3 Steinberg 2C: 1 Steinberg 3C: 1 Steinberg 4A: 1 Steinberg 4B: 2 Steinberg 4C: 5	Sickle Cell Disease	Multiple epiphyseal drilling and BMC implantation	25 months (12–47 months)	This treatment provides statistically significant improvement in hip pain and motion. 2 patients failed requiring further surgeries.	No complication was observed.
Ma et al. Stem Cell Res Ther 2014	Level I Randomized controlled clinical trial	39/49 Control group: 18/24 Treatment group: 21/25	35 (18–55) Control group: 34.8 Treatment group: 35.6	Ficat I: 7 Ficat II: 32 Ficat III: 10	Steroid: 26 Alcohol: 7 Idiopathic: 12	Control group: CD + autologous bone graft Treatment group: CD + autologous bone graft with BMC	24 months	Implantation of the autologous BMC grafting combined with CD is effective to prevent further progression for the early stages of AVN. Conversion to THR was required in 4 patients in control group and 2 patients in treatment group.	No complication was observed. The stage of AVN might affect the outcome, while etiological factors do not.
Chotivichit et al. J Med Assoc Thai 2014	Level IV Retrospective case series	32/34	31.9 (14–54)	Ficat II: 21 Ficat III: 13	Steroid: 26 SLE: 9 Idiopathic: 5	CD with bone marrow aspirate injection	24.6 months stage II 27.8 months stage III	CD + injection of bone marrow aspirate provides only fair results in stage II and III, with 4 THR in stage II and 5 THR in stage III.	This technique does not use concentration process.
Calori et al. Injury 2014	Level IV Retrospective case series	38/40	46.3 (21–73)	Ficat I: 7 Ficat II: 25 Ficat III: 8	Posttraumatic: 4 Steroid: 7 Idiopathic: 27	CD and implantation of bone marrow aspirate + growth factors (rhBMP-7) + scaffold of xenograft bone substitute was inserted inside the tunnel of the femur	36 months	CD + recombinant morphogenetic proteins + bone marrow aspirate + xenograft bone substitute decrease the incidence of fractal stage non-traumatic osteonecrosis and the progression of AVN and pain. 5 patients underwent THR.	4 cases of calcification in the soft tissue near the surgery access. 1 subtrochanteric fracture of the femur 1 week after CD.
Martin et al.	Level IV	49/73	43	Ficat I: 57	Steroid: 44		17 months		

Table 1 (continued)

Author	Level of evidence	Patient/hip treated	Age (years)	Staging	Etiology	Technique	Follow-up	Conclusions	Complications/notes
Croat Med J 2013	Retrospective case series			Ficat II: 16	Alcohol: 10 Idiopathic: 9 Other: 10	CD of the femoral head + adult BMC + PRP are injected into the area of osteonecrosis		This treatment provides a significant pain relief in 86% of patients, satisfactory results in patients with early stage AVN and can lead to complete resolution of the necrotic lesion. 16 hips underwent THR.	2 postoperative trochanteric bursitis at immediate F-up.
Mao et al. Bone 2013	Level IV Case series	62/78	36.3 (22–54)	Ficat I: 16 Ficat II: 52 Ficat III: 10	Steroid: 30 Alcohol: 27 Idiopathic: 9 Trauma: 12	Intra-arterial BMC via medial circumflex femoral artery	4.8 years (1–5 years)	The intra-arterial delivery of autologous BMC provides relief of symptoms, improves hip function and delays the progression of the disease. Only 6 hips requiring THR.	No complication was observed. The clinical outcome is better when it is applied prior to the collapse.
Lim et al. Exp Mol Med 2013	Level III Retrospective comparative study	128/190 Control group: 31 Treatment group: 159	Control group: 34.4 Treatment group: 36.3	Ficat IIa: 56 Ficat IIb: 47 Ficat III: 57	Steroid: 54 Alcohol: 24 Idiopathic: 25 Other: 4	Control group: CD, curettage and a bone graft Treatment group: Multiple drilling and BMC	87 months (8–134 months)	Comparable outcomes between multiple drilling + BMC implantation and CD techniques, with a failure rate of 43% and 45.2%, respectively.	Injected cells: 1.69×10^7 cells. Better results in patients who had more cells transplanted.
Rastogi et al. Musculoskelet Surg 2013	Level I Randomized controlled clinical trial	40/60 Control group: 30 Treatment group: 30	Control group: 33.0 Treatment group: 34.7 p: 0.47	–	Steroid: 18 Alcohol: 8 Idiopathic: 26 Smoking: 8	Control group: CD and unprocessed bone marrow injection Treatment group: CD + BMC implantation	24 months	Control and treatment group shows significant differences when compared with preoperative scores, without statistically significant inter-group differences in clinical scores. 3 conversion to THR only in the group treated with CD and unprocessed bone marrow injection.	No complications were noted in both groups. Transplanted cells: 1.1×10^8 cells.
Liu et al. Arch Orthop Trauma Surg 2013	Level III Retrospective comparative study	34/55 Control group: 27 Treatment group: 28	Control group: 38.1 Treatment group: 38.0	ARCO I: 5 ARCO IIb: 25 ARCO IIC: 30	Steroid: 19 Alcohol: 29 Idiopathic: 7	Control group: CD with implantation of porous nano-hydroxyapatite/polyamide 66 composite bone filler Treatment group: CD with implantation of BMC with porous nano-hydroxyapatite/polyamide 66 composite bone filler	Control: 24.9 Treatment: 26.7	CD + BMC treatment provides better outcomes respect to CD alone in decrease hip pain, improve hip function, preventing collapse of the femoral head, with 4 failures, compared to 5 in control group.	Ex vivo analysis.
Aarvold et al. Surgeon 2013	Level IV Case series	4/5	36.25	Ficat II: 5	Steroid: 3 Alcohol: 1 Idiopathic: 1	CD + impaction of BMC/milled allograft (obtained from frozen femoral heads) construct	44 months	This treatment shows the potential of BMC/allograft constructs for the treatment of early stage AVN.	
Kang et al. Yonsei Med J 2013	Level IV Case series	52/61	43.80 (19–66)	ARCO I: 5 ARCO II: 35 ARCO III: 18 ARCO IV: 3	Steroid: 6 Alcohol: 16 Idiopathic: 22 Trauma: 6	CD combined with auto iliac bone graft and implantation of BMC	68 months (60–88 months)	2 hips underwent THR. Overall clinical results of our procedure were not satisfactory, with 26 hip having bad or failed clinical results, particularly in patients with large lesions	Correlation between outcome and lesion size.
Pak et al. Pain Physician 2013	Level IV Case report	2	34 and 39	–	–	Injection of adipose tissue-derived stem cells with	12 months	The injection of stem cell mixture demonstrate the	Injected cells: 16×10^6 cells.

Table 1 (continued)

Author	Level of evidence	Patient/hip treated	Age (years)	Staging	Etiology	Technique	Follow-up	Conclusions	Complications/notes
Sen et al. J Arthroplasty 2012	Level I Randomized controlled clinical trial	40/51 Control group: 25 Treatment group: 26	–	ARCO I, II Mitchell A: 13 Mitchell B: 13 Mitchell C: 19 Mitchell D: 1 Steinberg Ic: 3 Steinberg IIa: 7 Steinberg IIb: 11 Steinberg IIc: 9 Steinberg IIa: 7 ARCO IC: 5 pt. ARCO IIA: 1 IIA: 30 pt. ARCO IIB: 46 pt. ARCO IIC: 23 pt. JOA I: 2 JOA 2: 4 JOA 3A: 1 JOA 3B: 2 ARCO I: 4 ARCO II: 20 Control group: 45.7 Treatment group: 42.2	Steroid: 14 Alcohol: 6 Idiopathic: 1 Pregnancy: 1 Cushing disease: 1 Trauma: 17	hyaluronic acid, PRP and CaCl ₂ to activate PRP. Then PRP + CaCl ₂ injection every 4 weeks Control group: CD alone Treatment group: CD + BMC implantation	24 months	presence of newly regenerated tissue in 2 severely necrotic femoral heads. BMC implantation can result in better clinical outcome and hip survival, with only 1 THR in treatment group vs 6 in control group.	No complications were observed. Better outcome in traumatic AVN than in non-traumatic AVN. Injected cells: 5×10^8 mononuclear cell to keep 5×10^7 CD34 ⁺ .
Civini et al. Int Orthop 2012	Level IV Case series	31/37	43.9 (24–56)	Steinberg Ic: 3 Steinberg IIa: 7 Steinberg IIb: 11 Steinberg IIc: 9 Steinberg IIa: 7 ARCO IC: 5 pt. ARCO IIA: 1 IIA: 30 pt. ARCO IIB: 46 pt. ARCO IIC: 23 pt. JOA I: 2 JOA 2: 4 JOA 3A: 1 JOA 3B: 2 ARCO I: 4 ARCO II: 20 Control group: 45.7 Treatment group: 42.2	Steroid: 14 Bone marrow transplantation: 4 Alcohol: 10 SLE: 1 Idiopathic: 6	CD + injection of BMC + new composite injectable bone substitute (PRO-DENSE®)	20.6 months (12–32 months)	Significant improvement of function and symptoms. 100% radiological success only in patient with stage I. This technique was best for early-stage lesions. 3 joints underwent THR.	No complications related to the procedure were seen during or after the operation.
Zhao et al. Bone 2012	Level I Randomized controlled clinical trial	93/97 Control group: 44 Treatment group: 53	33.1 (18–55)	ARCO IC: 5 pt. ARCO IIA: 1 IIA: 30 pt. ARCO IIB: 46 pt. ARCO IIC: 23 pt. JOA I: 2 JOA 2: 4 JOA 3A: 1 JOA 3B: 2 ARCO I: 4 ARCO II: 20 Control group: 45.7 Treatment group: 42.2	Steroid: 24 Alcohol: 19 Idiopathic: 30 Trauma: 20 Caisson disease: 11	Control group: CD alone Treatment group: CD with cultured bone-marrow derived MSC	60 months	Ex vivo expansion of bone-marrow derived MSC and implantation provides significantly improvement of pain and other joint symptoms and delay or avoid the progression of osteonecrosis and total hip replacement. 2 and 10 patients failed in treatment and control groups, respectively.	No complications were observed. Implanted cells: 2×10^6 cells.
Yoshioka et al. Int Orthop 2011	Level IV Case series	6/9	31.5 (16–52)	ARCO IC: 5 pt. ARCO IIA: 1 IIA: 30 pt. ARCO IIB: 46 pt. ARCO IIC: 23 pt. JOA I: 2 JOA 2: 4 JOA 3A: 1 JOA 3B: 2 ARCO I: 4 ARCO II: 20 Control group: 45.7 Treatment group: 42.2	Corticosteroid-induced AVN in SLE	CD + BMC implantation	41 months (37–53 months)	BMC treatment provides a significant improvement of pain and function, with 1 THR.	Implanted cells: 5.32×10^7 cells/ml.
Gangji et al. Bone 2011	Level I Double blinded controlled clinical trial	19/24 Control group: 11 Treatment group: 13	Control group: 45.7 Treatment group: 42.2	ARCO I: 4 ARCO II: 20 Control group: 45.7 Treatment group: 42.2	Steroid: 20 Alcohol: 2 Idiopathic: 2	Control group: CD alone Treatment group: CD + BMC implantation	60 months	BMC implantation in the necrotic lesion provides better results in early ON and delay its progression, reduces pain and decreases the volume of necrotic lesion. 2 patients failed in treatment group and 3 in control group.	No complications were observed.
Yamasaki et al. J Bone Joint Surg 2010	Level III Retrospective comparative study	30/39 Control group: 9 Treatment group: 30	Control group: 49 Treatment group: 41	JOA I: 2 JOA 2: 34 JOA 3A: 3 JOA 3B: 2 ARCO I: 4 ARCO II: 20 Control group: 45.7 Treatment group: 42.2	Steroid: 24 Alcohol: 10 Idiopathic: 5	Control group: Implantation of cell-free IP-CHA scaffold into the site of osteonecrosis Treatment group: Transplantation of BMC-seeded IP-CHA	Control: 31 months Treatment: 29 months	BMC treatment provide a progression of bone repair, accelerates revascularisation along the transition zone. This study described the apparent effectiveness of implantation of BMC with IP-CHA.	No intra- or postoperative complications were observed in either group.

Table 1 (continued)

Author	Level of evidence	Patient/hip treated	Age (years)	Staging	Etiology	Technique	Follow-up	Conclusions	Complications/notes
Wang et al. Arch Orthop Trauma Surg 2010	Level IV Case series	45/59	37.5 (16–56)	ARCO I: 2 ARCO IIA: 7 ARCO IIB: 13 ARCO IIC: 28 ARCO IIIA: 9	Steroid: 29 Alcohol: 22 Idiopathic: 8	CD + BMC implantation	27.6 months (12–40 months)	1 THR in treatment group vs. 3 in control group. CD + BMC significantly improved the joint pain, delayed the joint replacement and it is indicated for the treatment of stage I and II of AVN. 7 patients underwent THR.	No complications were seen during or after the operation. Worst outcome for steroid-induced AVN.
Hermigou et al. Indian J Orthop 2009	Level IV Case series	342/534	39 (16–61)	Steinberg I or II	Steroid: 102 Alcohol: 150 SCD: 282	CD + BMC implantation	13 years (8–18 y)	This treatment provide a complete resolution of AVN in 69 patients. THR was necessary in 94 hips.	Injected cells: 24×10^6 cells. Patient who receive high number of progenitor cells obtains better results.
Hendrich et al. Orthop Rev 2009	Level IV Case series	37	–	–	–	CD + BMC implantation	14 months (2–24 months)	Good results in AVN and safety were proved. Only 1 patient needs THR.	No specific complication.
Seyler et al. Clin Orthop Relat Res 2008	Level IV Case series	33/39	35 (18–52)	Ficat II: 22 Ficat III: 17	Steroid: 12 hips Alcohol: 8 hips SLE: 7 hips Tobacco: 4 hips Hepatitis C: 3 hips HIV: 2 hips Other: 3	CD with nonvascularized bone grafting procedures + OP-1 (BMP 7)	36 months (24–50 months)	Significant improvement of mean HHS. 13 failures. This is an effective and safe procedure.	
Yamasaki et al. Med Sci Monit 2008	Level IV Case report	2/4	Case 1: 18 Case 2: 40	ARCO II: 2 ARCO III: 2	Alcohol: 2 Idiopathic: 2	Transplantation of BMC into the affected area of one hip (left hip) using IP-CHA in two patients, while the other hip was simultaneously treated with transstrochanteric rotational osteotomy	22 months	Transplantation of BMC may provide a beneficial treatment for bone repair in the condition of ON. No failures were seen in this small sample.	1.9×10^9 bone-marrow mononuclear cell in case 1 and 2.7×10^9 in case 2. No progression of collapse.
Kawate et al. Artif Organs 2006	Level IV Case report	3/4	28 (25–30)	Steinberg Case 1: 4A Case 2: bil 4C Case 3: 4C	Steroid: 4 Alcohol: 2	Cultured bone-marrow derived MSC transplantation with b-TCP ceramics	34 months (27–48 months)	The MSCs/b-TCP transplantation provides a significant sclerotic change at the beginning. After 1 year it could be noted a revascularization, probably derived from the vascularized fibula. This procedure is not indicated for cases with severe preoperative collapse. No patient failed.	
Lieberman et al. Clin Orthop Relat Res 2004	Level IV Case series	15/17	47 (36–62)	Ficat IIA: 15 Ficat IIB: 1 Ficat III: 1	Steroid: 14 Alcohol: 4	CD + HBMP	53 months (26–94 months)	CD + Human bone morphogenetic protein provide relief of pain, delay the radiographic progression. 3 patients underwent THR.	
Gangji et al. J Bone Joint Surg 2004	Level II Prospective comparative study	13/18 Control Group: 8 Treatment Group: 10	Control Group: 48.8 Treatment Group: 40.9	ARCO I: 2 ARCO II: 16	Steroid: 14 Alcohol: 2 Idiopathic: 2	Control group: CD alone Treatment group: CD + BMC implantation	24 months	CD + BMC provide significant decrease in the level of pain, and other joint symptoms. The volume of necrotic lesions significantly improve only in treatment group.	

Table 1 (continued)

Author	Level of evidence	Patient/hip treated	Age (years)	Staging	Etiology	Technique	Follow-up	Conclusions	Complications/notes
Hermigou et al. Clin Orthop Relat Res 2002	Level IV Case series	116/189	31 (16–61)	Steinberg I: 59 Steinberg II: 86 Steinberg III: 12 Steinberg IV: 32	Steroid: 31 Alcohol: 56 Idiopathic: 10 SCD: 64 Organ transplantation: 21 Others: 7	CD + BMC implantation	7 years (5–11 years)	2 patients underwent THR in control group, whereas no patient failed in treatment group. Patients with hips in stage III and IV preoperatively had a poor results and progressed in stages. 34 patients failed and underwent THR.	No specific complication. Higher risk to failure for patients with corticosteroid treatment and stage III–IV. Correlation between the greater number of progenitor cell and smaller lesions with better outcomes. AVN etiology influences the results. Injected cells: 25×10^3 cells.

AVN avascular necrosis of the femoral head, CD core decompression, MSC mesenchymal stem cell, BMC bone marrow concentrate, ARCO Association Research Circulation Osseous, JOA Japanese Orthopedic Association, SCD sickle cell disease, SLE systemic lupus erythematosus, THR total hip replacement, IP-CHA interconnected porous calcium hydroxyapatite, G-CSF granulocyte-colony stimulating factor, rhBMP recombinant human bone morphogenetic protein, b-TCP beta-tricalcium phosphate, hUC-MSCs human umbilical cord-derived MSCs, LIPUS low-intensity pulsed ultrasound, PRP platelet-rich Plasma, HHS Harris Hip Score

articles [14, 32, 34, 41, 57], Steinberg classification in seven articles [18, 22, 31, 36, 40, 41, 45], and Mitchell classification in one article [30]. Overall, lesions of different stages, from early-stage AVN to collapsed head, were treated. Finally, evaluation time was also heterogeneous, with nine studies reporting short-term (<24 months follow-up), 32 medium-term (24–60 months), and seven long-term results (>60 months). The heterogeneity documented among studies may have influenced the results, as reported in some studies showing a better outcome for less severe and smaller lesions [21, 23, 29, 31, 40, 52, 54]. Other factors found to influence the final outcome were the number of transplanted cells [25, 36, 40] and etiology, with steroid-induced AVN showing poorer results [31, 40, 46] and traumatic AVN achieving better improvement than non-traumatic AVN [30].

Clinical results are reported in detail in Table 1. In summary, all 28 case series showed clinical score improvements, as well as good radiological and histological outcomes, with the only exceptions represented by the study by Chotivichit et al. [46], who showed short-term disease progression in 76% of the stage 2 and 69% of the stage 3 AVN after the injection of bone marrow aspirate, and the study by Kang et al. [29], who reported negative results in 26/61 hips at 68 months of follow-up.

Among comparative studies, seven were retrospective comparative studies [13, 15, 17, 25, 34, 54]: six missed to find any significant difference between treatment and control groups, analyzing clinical scores, radiologic outcomes and failures, and only one [27] reported significantly increased clinical and radiological scores, with fewer failures. Two level II prospective comparative studies [11, 39] were found in the literature. The study of Pilge et al. [11] performed a match-pair subanalysis of a RCT, but the number of patients was underpowered to obtain any significant difference. Conversely, Ganji et al. [39], although dealing with a very small survey of 18 hips, reported a significant increase in scores among patients treated with BMC, whereas patients treated only with CD did not significantly improve. Moreover, the failure rate of the treatment group was significantly lower than the control group.

The eight RCTs confirmed overall favourable results for the biological augmentation, with only two studies missing to find any significant difference. In detail, Pepke et al. [16] reported comparable clinical scores and failure rate, analyzing at two year' follow-up 11 hips treated with CD and BMC implantation against 14 hips treated with CD alone. Rastogi et al. [26] compared 30 hips treated with CD and unprocessed bone marrow with 30 hips treated with CD and BMC implantation, finding a significant difference in radiological score, but none in clinical scores. The other six RCTs [19, 23, 30, 33, 44, 50] reported a higher improvement of clinical and radiological outcomes in the groups treated with biological augmentation (four studies with BMC, one study with

Fig. 2 Publishing trend of studies on regenerative treatments for AVN, with the corresponding levels of evidence

cultured bone-marrow derived MSC, and one study with intra-arterial injection of peripheral blood MSC).

The meta-analysis of failures with the Kaplan-Mayer analysis among 1467 patients analyzed in 41 studies (excluding studies not reporting the number or the time of failures) showed a total estimated cumulative survivorship of 89.1% at 24 months of follow-up, 81.9% at 60 months of follow-up, and 80% at 120 months of follow-up, confirming overall good results and durability for biological therapies (Fig. 3).

Finally, in order to make a comparative evaluation of homogeneous treatment and control groups, a meta-analysis was performed including only level 1 RCT dealing with stem cell augmentation [16, 19, 23, 26, 30, 33, 44, 50]. The total estimated cumulative survivorship for biological therapies and control group was of 95.6 vs. 85.7% at 24 months of follow-up and 89.9 vs. 70.6% at 60 months of follow-up, with a statistically significant difference between the two curves ($p < 0.0001$, evaluated with the log rank method), showing

the benefit of regenerative therapies compared to CD to provide longer lasting results for the treatment of AVN (Fig. 4).

Discussion

The main finding of this study is that regenerative therapies offer a higher survivorship over time compared to control group for the treatment of AVN, as demonstrated by a level I meta-analysis.

This systematic review allowed to document several regenerative procedures. Biological therapies to address AVN were introduced in the clinical practice in the 1990s, aiming at improving the results of CD [6]. In particular, stem cell-based therapies have been used with the rationale of enhancing the effect of core decompression by promoting bone formation in AVN [6]. Different factors may explain the effectiveness of BMC [59, 60]: the presence of stem cells endowed with osteogenic properties, the secretion of angiogenic cytokines, resulting in increased angiogenesis and subsequent improvement in osteogenesis, as well as the presence of endothelial cell progenitors actively engaged in neoangiogenesis from the pre-existing capillaries and able to enhance the generation of pericytes and vascular mural cells [6].

Aside from BMC, this systematic review documented several other regenerative techniques, proposed in the last 20 years to improve AVN healing. These include implantation of other types of MSC (like adipose-tissue derived or allogeneic human umbilical cord-derived MSCs) in the osteonecrotic area, intra-arterial injection of MSCs, implantation of bioactive molecules (recombinant human bone morphogenetic protein or growth factors), and PRP. They were used to treat extremely heterogeneous AVN conditions in heterogeneous populations and, at the moment, no

Fig. 3 Survivorship curve of 1467 patients treated with regenerative procedures

Fig. 4 Comparison between the survivorship curves of patients treated with biological therapies (black line) vs. control group (gray line)

recommendation can be made on the most efficient treatment or on the best indications [61]. Nevertheless, a meta-analysis of the survivorship curve among 1467 patients analyzed in 41 studies showed an overall total estimated cumulative survivorship of 80% at 120 months of follow-up, confirming good results and durability for the biological augmentation approach.

The interest in regenerative therapies for AVN is rising, with growing evidence provided by the increasing number of published case series, RCT, reviews, and meta-analysis, with particular focus on results of cell-based therapies. Literature evidence has been analyzed in the past few years, with several authors supporting the overall benefit both in term of clinical and radiological outcomes.

In 2014, Li et al. [62] published a meta-analysis including one RCT and one comparative study, reporting a significant improvement in clinical outcomes, evaluated with the Harris hip score (HHS). Later in the same year, Lau et al. [4] published a systematic review on five studies, including three RCTs reporting better clinical results, and two reporting better radiological results for CD and BMC compared to CD alone. In 2016, three meta-analyses were published on the use of cell therapy combined with CD for the treatment of AVN. Clinical results were analyzed by Yuan et al. [63], who included one RCT and three comparative studies and found a significant difference in HHS between treatment and control groups. They also demonstrated an improvement of radiological outcome, in terms of AVN progression, including six articles, two of which were RCT. This result was also confirmed by Villa et al. [64] on two RCT, and by Papakostidis et al. [65], who included three RCTs and three comparative studies to document a reduced rate of femoral head collapse. Finally, in a recent systematic review, Piuze et al. [66] included 11 comparative studies, 8 of which were RCTs. They concluded that cell therapies led to a significant clinical

improvement in 7/11 comparative studies and a better radiological outcome in 8/11 studies.

While all the aforementioned literature reviews and analysis agree on an overall positive outcome in terms of symptomatic relief and functional improvement, reflected in the different clinical scores, and of radiographic appearance of the femoral heads after regenerative treatments, only a weaker evidence supported possible benefits in terms of failures. The reduction of the number of failures, defined as the need to undergo THR, can actually be considered the most important goal in this type of patients. In fact, the durability of THR is a concern in such young patients, with a considerable risk for revision arthroplasty during their lifetime. Therefore, the success of non-replacement procedures is of key importance both for patients' quality of life and for the impact on the health care system and society.

Failures were analyzed in two systematic reviews, which reported that the majority of the current literature found a lower number of THR in patients treated with CD and cell therapy compared with patients treated with CD alone [4, 66]. Meta-analysis articles, however, were not able to provide strong evidence to confirm these findings. In fact, Villa et al. [64] included in the analysis two RCTs and were not able to find a significant difference. Similarly, Papakostidis et al. [65] performed a meta-analysis of failures on six comparative studies, but they only found a tendency for cell therapy against CD alone. Only Yuan et al. [63] were able to demonstrate a significant decrease in failures in hips treated with both CD and BMC, but with the limits of a meta-analysis including three retrospective comparative studies and therefore low study level. This is not of secondary importance, since a direct correlation between low study quality and positive results has been demonstrated in the literature [67].

The present study was able to document, for the first time with methodologically strong level I analysis, that the use of

regenerative therapies can reduce the number of failures compared to CD alone. The Kaplan-Mayer method was used to perform a meta-analysis of eight level I RCTs in order to calculate and compare the survivorship of control and treatment groups. At medium-term follow-up, 89.9% of hips treated with CD and regenerative therapies survived, against 70.6% of hips treated with CD alone.

This meta-analysis still presents some limitations. The first one is represented by the heterogeneity of the populations analyzed, with heterogeneous lesion stages, etiologies, and patient characteristics. Anyway, this limit is overtaken in the level I meta-analysis that represents a comparison between control and treatment groups which were homogeneous inside the single RCT. However, residual heterogeneity among the whole populations does not allow to draw conclusions about patients who could get the maximum benefit from the procedures. Another methodological limitation is the inclusion of a time interval for failures, which limits the value of the survivorship curve in studies with short follow-up; nonetheless, this is not of primary matter for a treatment which is intended to last decades. Moreover, AVN was evaluated with different systems, which introduces variability in the interpretation of the results. Finally, the included studies described results of different treatments (even though the meta-analysis focused on RCT, all regarding stem cell-based therapies), which may have different success rates. In addition, there is a lack of homogeneity among control groups, sometimes chosen as CD alone, sometimes as CD plus not concentrated bone marrow aspirate. Indeed, at the present moment, the BMC approach itself lacks standardization with respect to the quantitative and qualitative characterization of methods for cell harvest, cell processing, and cell transplantation/delivery, as described in a recent review by Piuze et al. [68]. Therefore, it is not possible to propose a regenerative therapy against the others, and neither there is evidence to understand if the ideal treatment could include more than one single therapy, creating a biologic chamber using the “diamond concept” for bone healing [69]. Moreover, PEMF and hyperbaric oxygen therapy may represent suitable options for the earlier stages [70], and future studies should further explore their potential and treatment indication, alone or in combination with the emerging regenerative options. However, this analysis still allowed to draw interesting conclusions on the potential of biological treatments.

This systematic review documented a growing interest on regenerative therapies for the treatment of AVN. Overall, they offer good clinical results, with an overall survivorship rate of 80% at ten years. The level I meta-analysis showed that the combination of CD with regenerative techniques provides a significant improvement in terms of survivorship over time compared to CD alone. Further studies are needed to identify the best procedure and the most suitable patients to benefit from regenerative treatments for AVN.

Acknowledgements The authors thank Elettra Pignotti for the assistance in the statistical analysis and Lucia Mancini for English editing.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Malizos KN, Karantanas AH, Varitimidis SE, Dailiana ZH, Bargiotas K, Maris T (2007) Osteonecrosis of the femoral head: etiology, imaging and treatment. *Eur J Radiol* 63:16–28. <https://doi.org/10.1016/j.ejrad.2007.03.019>
2. Parsons SJ, Steele N (2007) Osteonecrosis of the femoral head: part 1—etiology, pathogenesis, investigation, classification. *Curr Orthop* 21:457–463. <https://doi.org/10.1016/j.cuor.2007.11.004>
3. Wang GJ, Cui Q, Balian G (2000) The Nicolas Andry award. The pathogenesis and prevention of steroid-induced osteonecrosis. *Clin Orthop Relat Res*:295–310
4. Lau RL, Perruccio AV, Evans HM, Mahomed SR, Mahomed NN, Gandhi R (2014) Stem cell therapy for the treatment of early stage avascular necrosis of the femoral head: a systematic review. *BMC Musculoskelet Disord* 15:156. <https://doi.org/10.1186/1471-2474-15-156>
5. Sun Y, Feng Y, Zhang C (2009) The effect of bone marrow mononuclear cells on vascularization and bone regeneration in steroid-induced osteonecrosis of the femoral head. *Joint Bone Spine* 76: 685–690. <https://doi.org/10.1016/j.jbspin.2009.04.002>
6. Hernigou P, Trousselier M, Roubineau F et al (2016) Stem cell therapy for the treatment of hip osteonecrosis: a 30-year review of progress. *Clin Orthop Surg* 8:1–8. <https://doi.org/10.4055/cios.2016.8.1.1>
7. Mont MA, Carbone JJ, Fairbank AC (1996) Core decompression versus nonoperative management for osteonecrosis of the hip. *Clin Orthop Relat Res* 324:169–178
8. Moher D, Liberati A, Tetzlaff J, Altman DG (2009) Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ* 339:b2535. <https://doi.org/10.1136/bmj.b2535>
9. Stewart LA (2002) Chemotherapy in adult high-grade glioma: a systematic review and meta-analysis of individual patient data from 12 randomised trials. *Lancet* 359:1011–1018
10. Tian DH, De Silva RP, Wang T, Yan TD (2014) Open surgical repair for chronic type B aortic dissection: a systematic review. *Ann Cardiothorac Surg* 3:340–350. <https://doi.org/10.3978/j.issn.2225-319X.2014.07.10>
11. Pilge H, Bittersohl B, Schnependahl J et al (2016) Bone marrow aspirate concentrate in combination with intravenous iloprost increases bone healing in patients with avascular necrosis of the femoral head: a matched pair analysis. *Orthop Rev (Pavia)* 8:6902. <https://doi.org/10.4081/or.2016.6902>
12. Gao F, Sun W, Guo W, Wang B, Cheng L, Li Z (2016) Combined with bone marrow-derived cells and rhBMP-2 for osteonecrosis after femoral neck fractures in children and adolescents: a case series. *Sci Rep* 6:30730. <https://doi.org/10.1038/srep30730>
13. Gianakos AL, Moya-Angeler J, Duggal S et al (2016) The efficacy of bisphosphonates with core decompression and mesenchymal stem cells compared with bisphosphonates alone in the treatment of osteonecrosis of the hip: a retrospective study. *HSS J* 12:137–144. <https://doi.org/10.1007/s11420-016-9487-7>
14. Mishima H, Sugaya H, Yoshioka T et al (2016) The safety and efficacy of combined autologous concentrated bone marrow

- grafting and low-intensity pulsed ultrasound in the treatment of osteonecrosis of the femoral head. *Eur J Orthop Surg Traumatol* 26:293–298. <https://doi.org/10.1007/s00590-016-1752-4>
15. Yan D, Chen L, Li Z, Guo W, Sun W (2015) Autologous mesenchymal stem cell implantation in the management of osteonecrosis of the femoral head. *Curr Orthop Pract* 26:265–268. <https://doi.org/10.1097/bco.0000000000000218>
 16. Pepke W, Kasten P, Beckmann NA, Janicki P, Egermann M (2016) Core decompression and autologous bone marrow concentrate for treatment of femoral head osteonecrosis: a randomized prospective study. *Orthop Rev (Pavia)* 8:6162. <https://doi.org/10.4081/or.2016.6162>
 17. Cruz-Pardos A, Garcia-Rey E, Ortega-Chamarro JA, Duran-Manrique D, Gomez-Barrena E (2016) Mid-term comparative outcomes of autologous bone-marrow concentration to treat osteonecrosis of the femoral head in standard practice. *Hip Int* 26:432–437. <https://doi.org/10.5301/hipint.5000366>
 18. Persiani P, De Cristo C, Graci J, Noia G, Gurzi M, Villani C (2015) Stage-related results in treatment of hip osteonecrosis with core-decompression and autologous mesenchymal stem cells. *Acta Orthop Belg* 81:406–412
 19. Tabatabaee RM, Saberi S, Parvizi J, Mortazavi SM, Farzan M (2015) Combining concentrated autologous bone marrow stem cells injection with Core decompression improves outcome for patients with early-stage osteonecrosis of the femoral head: a comparative study. *J Arthroplast* 30:11–15. <https://doi.org/10.1016/j.arth.2015.06.022>
 20. Daltro GC, Fortuna V, de Souza ES et al (2015) Efficacy of autologous stem cell-based therapy for osteonecrosis of the femoral head in sickle cell disease: a five-year follow-up study. *Stem Cell Res Ther* 6:110. <https://doi.org/10.1186/s13287-015-0105-2>
 21. Wang T, Wang W, Yin ZS (2014) Treatment of osteonecrosis of the femoral head with thorough debridement, bone grafting and bone-marrow mononuclear cells implantation. *Eur J Orthop Surg Traumatol* 24:197–202. <https://doi.org/10.1007/s00590-012-1161-2>
 22. Novais EN, Sankar WN, Wells L, Carry PM, Kim YJ (2015) Preliminary results of multiple epiphyseal drilling and autologous bone marrow implantation for osteonecrosis of the femoral head secondary to sickle cell disease in children. *J Pediatr Orthop* 35:810–815. <https://doi.org/10.1097/BPO.0000000000000381>
 23. Ma Y, Wang T, Liao J et al (2014) Efficacy of autologous bone marrow buffy coat grafting combined with core decompression in patients with avascular necrosis of femoral head: a prospective, double-blinded, randomized, controlled study. *Stem Cell Res Ther* 5:115. <https://doi.org/10.1186/srct505>
 24. Martin JR, Houdek MT, Sierra RJ (2013) Use of concentrated bone marrow aspirate and platelet rich plasma during minimally invasive decompression of the femoral head in the treatment of osteonecrosis. *Croat Med J* 54:219–224
 25. Lim YW, Kim YS, Lee JW, Kwon SY (2013) Stem cell implantation for osteonecrosis of the femoral head. *Exp Mol Med* 45:e61. <https://doi.org/10.1038/emm.2013.128>
 26. Rastogi S, Sankineani SR, Nag HL et al (2013) Intralesional autologous mesenchymal stem cells in management of osteonecrosis of femur: a preliminary study. *Musculoskelet Surg* 97:223–228. <https://doi.org/10.1007/s12306-013-0273-0>
 27. Liu Y, Liu S, Su X (2013) Core decompression and implantation of bone marrow mononuclear cells with porous hydroxylapatite composite filler for the treatment of osteonecrosis of the femoral head. *Arch Orthop Trauma Surg* 133:125–133. <https://doi.org/10.1007/s00402-012-1623-3>
 28. Aarvold A, Smith JO, Tayton ER et al (2013) A tissue engineering strategy for the treatment of avascular necrosis of the femoral head. *Surgeon* 11:319–325. <https://doi.org/10.1016/j.surge.2013.02.008>
 29. Kang JS, Moon KH, Kim BS et al (2013) Clinical results of autologous cancellous bone grafts combined with implantation of autologous bone marrow cells for osteonecrosis of the femoral head: a minimum 5-year follow-up. *Yonsei Med J* 54:510–515. <https://doi.org/10.3349/ymj.2013.54.2.510>
 30. Sen RK, Tripathy SK, Aggarwal S, Marwaha N, Sharma RR, Khandelwal N (2012) Early results of core decompression and autologous bone marrow mononuclear cells instillation in femoral head osteonecrosis. a randomized control study *J Arthroplasty* 27:679–686. <https://doi.org/10.1016/j.arth.2011.08.008>
 31. Civinini R, De Biase P, Carulli C et al (2012) The use of an injectable calcium sulphate/calcium phosphate bioceramic in the treatment of osteonecrosis of the femoral head. *Int Orthop* 36:1583–1588. <https://doi.org/10.1007/s00264-012-1525-6>
 32. Yoshioka T, Mishima H, Akaogi H, Sakai S, Li M, Ochiai N (2011) Concentrated autologous bone marrow aspirate transplantation treatment for corticosteroid-induced osteonecrosis of the femoral head in systemic lupus erythematosus. *Int Orthop* 35:823–829. <https://doi.org/10.1007/s00264-010-1048-y>
 33. Gangji V, De Maertelaer V, Hauzeur JP (2011) Autologous bone marrow cell implantation in the treatment of non-traumatic osteonecrosis of the femoral head: five year follow-up of a prospective controlled study. *Bone* 49:1005–1009. <https://doi.org/10.1016/j.bone.2011.07.032>
 34. Yamasaki T, Yasunaga Y, Ishikawa M, Hamaki T, Ochi M (2010) Bone-marrow-derived mononuclear cells with a porous hydroxyapatite scaffold for the treatment of osteonecrosis of the femoral head: a preliminary study. *J Bone Joint Surg Br* 92:337–341. <https://doi.org/10.1302/0301-620X.92B3.22483>
 35. Wang BL, Sun W, Shi ZC et al (2010) Treatment of nontraumatic osteonecrosis of the femoral head with the implantation of core decompression and concentrated autologous bone marrow containing mononuclear cells. *Arch Orthop Trauma Surg* 130:859–865. <https://doi.org/10.1007/s00402-009-0939-0>
 36. Hernigou P, Poignard A, Zilber S, Rouard H (2009) Cell therapy of hip osteonecrosis with autologous bone marrow grafting. *Indian J Orthop* 43:40–45. <https://doi.org/10.4103/0019-5413.45322>
 37. Hendrich C, Franz E, Waertel G, Krebs R, Jager M (2009) Safety of autologous bone marrow aspiration concentrate transplantation: initial experiences in 101 patients. *Orthop Rev (Pavia)* 1:e32. <https://doi.org/10.4081/or.2009.e32>
 38. Yamasaki T, Yasunaga Y, Terayama H et al (2008) Transplantation of bone marrow mononuclear cells enables simultaneous treatment with osteotomy for osteonecrosis of the bilateral femoral head. *Med Sci Monit* 14:CS23–CS30
 39. Gangji V, Hauzeur JP, Matos C, De Maertelaer V, Toungouz M, Lambermont M (2004) Treatment of osteonecrosis of the femoral head with implantation of autologous bone-marrow cells. A pilot study *J Bone Joint Surg Am* 86-A:1153–1160
 40. Hernigou P, Beaujean F (2002) Treatment of osteonecrosis with autologous bone marrow grafting. *Clin Orthop Relat Res*:14–23
 41. Aoyama T, Fujita Y, Madoba K et al (2015) Rehabilitation program after mesenchymal stromal cell transplantation augmented by vascularized bone grafts for idiopathic osteonecrosis of the femoral head: a preliminary study. *Arch Phys Med Rehabil* 96:532–539. <https://doi.org/10.1016/j.apmr.2014.09.040>
 42. Zhao D, Liu B, Wang B et al (2015) Autologous bone marrow mesenchymal stem cells associated with tantalum rod implantation and vascularized iliac grafting for the treatment of end-stage osteonecrosis of the femoral head. *Biomed Res Int* 2015:240506. <https://doi.org/10.1155/2015/240506>
 43. Aoyama T, Goto K, Kakinoki R et al (2014) An exploratory clinical trial for idiopathic osteonecrosis of femoral head by cultured autologous multipotent mesenchymal stromal cells augmented with vascularized bone grafts. *Tissue Eng Part B Rev* 20:233–242. <https://doi.org/10.1089/ten.TEB.2014.0090>

44. Zhao D, Cui D, Wang B et al (2012) Treatment of early stage osteonecrosis of the femoral head with autologous implantation of bone marrow-derived and cultured mesenchymal stem cells. *Bone* 50:325–330. <https://doi.org/10.1016/j.bone.2011.11.002>
45. Kawate K, Yajima H, Ohgushi H et al (2006) Tissue-engineered approach for the treatment of steroid-induced osteonecrosis of the femoral head: transplantation of autologous mesenchymal stem cells cultured with beta-tricalcium phosphate ceramics and free vascularized fibula. *Artif Organs* 30:960–962. <https://doi.org/10.1111/j.1525-1594.2006.00333.x>
46. Chotivichit A, Korwutthikulrangsri E, Pornrattanamaneewong C, Achawakulthep C (2014) Core decompression with bone marrow injection for the treatment of femoral head osteonecrosis. *J Med Assoc Thai* 97(Suppl 9):S139–S143
47. Calori GM, Mazza E, Colombo M, Mazzola S, Mineo GV, Giannoudis PV (2014) Treatment of AVN using the induction chamber technique and a biological-based approach: indications and clinical results. *Injury* 45:369–373. <https://doi.org/10.1016/j.injury.2013.09.014>
48. Pak J (2012) Autologous adipose tissue-derived stem cells induce persistent bone-like tissue in osteonecrotic femoral heads. *Pain Physician* 15:75–85
49. Gao HY, Zhang GP, Wang J et al (2015) Clinical Effects of Novel Nanoscaled Core Decompression Rods Combined with Umbilical Cord Mesenchymal Stem Cells on the Treatment of Early Osteonecrosis of the Femoral Head. *J Nanomater* 2015:902836. <https://doi.org/10.1155/2015/902836>
50. Mao Q, Wang W, Xu T et al (2015) Combination treatment of biomechanical support and targeted intra-arterial infusion of peripheral blood stem cells mobilized by granulocyte-colony stimulating factor for the osteonecrosis of the femoral head: a randomized controlled clinical trial. *J Bone Miner Res* 30:647–656. <https://doi.org/10.1002/jbmr.2390>
51. Chen C, Qu Z, Yin X et al (2016) Efficacy of umbilical cord-derived mesenchymal stem cell-based therapy for osteonecrosis of the femoral head: a three-year follow-up study. *Mol Med Rep* 14: 4209–4215. <https://doi.org/10.3892/mmr.2016.5745>
52. Mao Q, Jin H, Liao F, Xiao L, Chen D, Tong P (2013) The efficacy of targeted intraarterial delivery of concentrated autologous bone marrow containing mononuclear cells in the treatment of osteonecrosis of the femoral head: a five year follow-up study. *Bone* 57:509–516. <https://doi.org/10.1016/j.bone.2013.08.022>
53. Cai J, Wu Z, Huang L et al (2014) Cotransplantation of bone marrow mononuclear cells and umbilical cord mesenchymal stem cells in avascular necrosis of the femoral head. *Transplant Proc* 46:151–155. <https://doi.org/10.1016/j.transproceed.2013.06.021>
54. Sun W, Li Z, Gao F, Shi Z, Zhang Q, Guo W (2014) Recombinant human bone morphogenetic protein-2 in debridement and impacted bone graft for the treatment of femoral head osteonecrosis. *PLoS One* 9:e100424. <https://doi.org/10.1371/journal.pone.0100424>
55. Seyler TM, Marker DR, Ulrich SD, Fatscher T, Mont MA (2008) Nonvascularized bone grafting defers joint arthroplasty in hip osteonecrosis. *Clin Orthop Relat Res* 466:1125–1132. <https://doi.org/10.1007/s11999-008-0211-x>
56. Lieberman JR, Conduah A, Urist MR (2004) Treatment of osteonecrosis of the femoral head with core decompression and human bone morphogenetic protein. *Clin Orthop Relat Res*:139–145
57. Kuroda Y, Asada R, So K et al (2016) A pilot study of regenerative therapy using controlled release of recombinant human fibroblast growth factor for patients with pre-collapse osteonecrosis of the femoral head. *Int Orthop* 40:1747–1754. <https://doi.org/10.1007/s00264-015-3083-1>
58. Samy AM (2016) Management of osteonecrosis of the femoral head: a novel technique. *Indian J Orthop* 50:359–365. <https://doi.org/10.4103/0019-5413.185590>
59. Murphy MB, Moncivais K, Caplan AI (2013) Mesenchymal stem cells: environmentally responsive therapeutics for regenerative medicine. *Exp Mol Med* 45:e54. <https://doi.org/10.1038/emmm.2013.94>
60. Hemigou P (2015) Bone transplantation and tissue engineering, part IV. Mesenchymal stem cells: history in orthopedic surgery from Cohnheim and Goujon to the Nobel Prize of Yamanaka. *Int Orthop* 39:807–817. <https://doi.org/10.1007/s00264-015-2716-8>
61. Calori GM, Mazza E, Colombo A, Mazzola S, Colombo M (2017) Core decompression and biotechnologies in the treatment of avascular necrosis of the femoral head. *EFORT Open Rev* 2:41–50. <https://doi.org/10.1302/2058-5241.2.150006>
62. Li X, Xu X, Wu W (2014) Comparison of bone marrow mesenchymal stem cells and core decompression in treatment of osteonecrosis of the femoral head: a meta-analysis. *Int J Clin Exp Pathol* 7:5024–5030
63. Yuan HF, Zhang J, Guo CA, Yan ZQ (2016) Clinical outcomes of osteonecrosis of the femoral head after autologous bone marrow stem cell implantation: a meta-analysis of seven case-control studies. *Clinics (Sao Paulo)* 71:110–113. [https://doi.org/10.6061/clinics/2016\(02\)10](https://doi.org/10.6061/clinics/2016(02)10)
64. Villa JC, Husain S, van der List JP, Gianakos A, Lane JM (2016) Treatment of pre-collapse stages of osteonecrosis of the femoral head: a systematic review of randomized control trials. *HSS J* 12: 261–271. <https://doi.org/10.1007/s11420-016-9505-9>
65. Papakostidis C, Tosounidis TH, Jones E, Giannoudis PV (2016) The role of “cell therapy” in osteonecrosis of the femoral head. A systematic review of the literature and meta-analysis of 7 studies. *Acta Orthop* 87:72–78. <https://doi.org/10.3109/17453674.2015.1077418>
66. Piuze NS, Chahla J, Schrock JB et al (2017) Evidence for the use of cell-based therapy for the treatment of osteonecrosis of the femoral head: a systematic review of the literature. *J Arthroplast* 32:1698–1708. <https://doi.org/10.1016/j.arth.2016.12.049>
67. Serner A, van Eijck CH, Beumer BR, Holmich P, Weir A, de Vos RJ (2015) Study quality on groin injury management remains low: a systematic review on treatment of groin pain in athletes. *Br J Sports Med* 49:813. <https://doi.org/10.1136/bjsports-2014-094256>
68. Piuze NS, Chahla J, Jiandong H et al (2017) Analysis of cell therapies used in clinical trials for the treatment of osteonecrosis of the femoral head: a systematic review of the literature. *J Arthroplast* 32: 2612–2618. <https://doi.org/10.1016/j.arth.2017.02.075>
69. Giannoudis PV, Einhorn TA, Marsh D (2007) Fracture healing: the diamond concept. *Injury* 38(Suppl 4):S3–S6
70. Osmani F, Thakkar S, Vigdorchik J (2017) The utility of conservative treatment modalities in the Management of Osteonecrosis. *Bull Hosp Jt Dis* (2013) 75:186–192