Investigational regenerative medicine for non-traumatic osteonecrosis of the femoral head: a survey of registered clinical trials

Abstract

Introduction

Osteonecrosis of the femoral head (ONFH) is a refractory disease requiring joint replacement in young patients. Regenerative therapies have been developed.

Areas covered

This study surveyed clinical trials on regenerative medicine for ONFH. We extracted clinical trials on non-traumatic ONFH from the websites of five publicly available major registries (European Union Clinical Trials Register ([EU-CTR], ClinicalTrials.gov, Chinese Clinical Trial Registry [ChiCTR], University Hospital Medical Information Network–Clinical Trial Registry [UMIN-CTR] and Australian New Zealand Clinical Trials Registry [ANZCTR]). The trials were classified into six categories based on purpose: surgical treatment, non-drug conservative treatment, conservative drug treatment, therapeutic strategy, diagnosis and pathogenesis, and regenerative therapy.) We extracted 169 clinical trials on ONFH. Of these, 37 were on regenerative medicine, including 29 on cell therapy. Surgical treatment was the most common treatment, followed by regenerative therapy. There were 9 clinical trials registered in the EU-CTR, with 5 on regenerative medicine; 79 trials registered on ClinicalTrials.gov, with 24 on regenerative medicine; 54 trials registered in the ChiCTR, with 6 on regenerative medicine.

Expert opinion

The focus of the joint-preserving surgery has shifted to regenerative therapy based on using cell therapy in early-stage ONFH. The global standardisation of regenerative therapy is still ongoing.

Keywords

avascular necrosis, cell therapy, clinical trial, osteonecrosis of the femoral head, regenerative therapy, registry

Article highlights

・ONFH is a refractory joint disease that causes femoral head collapse, pain, limitation of hip motion and gait disability.

・ONFH is the main reason for THA in young generation. Younger patients are hesitant to undergo artificial joint surgery due to its restrictions on sports activity, the lifelong risks of infection and dislocation, high medical costs and potential for further revision surgery.

・As with the SARS outbreak, attention needs to be paid to a possible rapid increase in corticosteroid-associated ONFH after the COVID-19 pandemic.

・Regenerative medicine modified CD is considered the next treatment of interest to preserve hip joints. However, there has been limited validation for these newer regenerative therapies.

・This study surveyed clinical trials on regenerative medicine for ONFH. There were 37 clinical trials on regenerative medicine, including 29 on cell therapy.

Background

Osteonecrosis of the femoral head (ONFH) is an intractable disease of the hip affecting young people. Systemic corticosteroid pulse therapy and heavy alcohol consumption are the main factors in non-traumatic ONFH development. The number of patients with corticosteroid-induced ONFH substantially increased in China after systemic administration of corticosteroids for pneumonia due to severe acute respiratory syndrome (SARS) in 2003. This is similar to the current situation with coronavirus disease 2019 (COVID-19) pneumonia, and there is concern about a rapid increase in ONFH patients after COVID-19 treatment [1–3]. ONFH pathogenesis involves a critical loss of vascular supply to the femoral head, characterised by empty lacunae on osteocytes, although the aetiology of non-traumatic ONFH is multi-factorial and unclear [4–7]. ONFH occurs around 40 years of age and is the main reason young patients undergo total hip arthroplasty (THA). THA is the optimal final treatment for end-stage osteoarthritis (OA) due to femoral head collapse. Good results of THA in ONFH patients have been reported, comparable to results of THA in OA patients [8]. The improved, long-term results of THA in ONFH patients are largely due to improved surgical techniques and revolutionary improvements in implant quality, such as the advent of highly cross-linked polyethylene [9]. Therefore, physicians easily choose THA for young ONFH patients; in the last two decades, more than 90% of ONFH patients in the U.S. [10] and more than 70% in Japan [12] underwent THA. However, for young ONFH patients, THA is not an ideal solution due to further revision surgeries, restrictions on sports activity, high risk of dislocation, lifelong risk of periprosthetic joint infection and high medical costs. Therefore, the ideal goal of ONFH treatment is to preserve the hip joint, avoid femoral collapse head and delay THA. Current guidelines

on ONFH worldwide [4–7, 13] do not provide a consensus on the strategy of joint-preserving surgery. Historically, core decompression (CD) and bone grafting (BG) were used to preserve joints in the West, while osteotomy was developed and used in Japan and the rest of Asia. In Japan, for 50 years, osteotomy has been the preferred surgical treatment of choice for joint preservation, and the long-term results have been clarified [5, 11]. The idea behind osteotomy is to move the necrotic area from weight bearing regions of the femoral head. These procedures are technically demanding and less commonly used in U.S. [4, 12], but they are found to be popular in Asia [12, 13]. We previously reported the difference in the therapeutic strategy for joint-preserving surgery for non-traumatic ONFH between the U.S. and Japan [10, 12]. Joint-preserving surgeries, such as osteotomy and vascularised BG, are gradually decreasing due to technical demands, long hospitalisation, and difficulty in conversion to THA. However, in Europe and the U.S., CD is popular because it is percutaneous, less surgically invasive, does not require hospitalisation and can be easily converted to THA. Since around 2000, various CD-based clinical trials on regenerative medicine have emerged and been conducted as next-generation treatment for ONFH.

Registration of clinical trials in public registries is necessary in the field of orthopaedics. In July 2005, the International Committee of Medical Journal Editors (ICMJE), the *British Medical Journal* and members of major medical journals, such as the *New England journal*, the *Lancet* and *JAMA*, began to require registration of prospective clinical trials involving human participants before beginning the trials as a prerequisite for publication in its member journals [14], due to the tendency to hide failed clinical results and only publish good results in top medical journals. The pre-registration system for clinical trials was introduced in the U.S. and Canada in the nineties and has

since been introduced in many countries. The U.S. National Library of Medicine at the National Institutes of Health (Bethesda, MD, USA) maintains the largest clinical trial registry, ClinicalTrials.gov [15], which has registered more than 469,667 research studies in all 50 U.S. states and in 222 countries. Section 801 of the 2007 US Food and Drug Administration Amendments Act (FDAAA) [16] requires sponsors of clinical trials on FDA-regulated products to register the information about the trials on ClinicalTrials.gov before initiating them. The FDAAA levies a penalty for failure to submit a certificate of registration or results information when applying for approval. The obligation to disclose registrations has been incorporated into the Declaration of Helsinki since its 2008 revision, and the 2013 revision extends it to all research covered by the declaration, not just clinical trials. In 2005, the World Health Organisation (WHO) established the International Clinical Trial Registry Platform (ICTRP), a system that allows users to search for clinical trial information from around the world. The ICTRP Registry Network started in 2006 with 3 registries and now has 18 mostly national or regional registries and is continuously growing. The network follows a set of published standards defined and agreed upon by it. It currently has ~19,500 clinical trials and provides updated clinical trial records to the ICTRP on a weekly basis. In response to the global movement for clinical trial registration triggered by the ICMJE, the University Hospital Medical Information Network (UMIN) established the first ICMJE-approved clinical trial registry, the UMIN-Clinical Trial Registry (UMIN-CTR) [17], in Japan in 2005. In China, the Chinese Clinical Trial Registry (ChiCTR) [18] was established in 2005, and the Ministry of Health of China assigned it to be the representative of China to join the WHO ICTRP in 2007. The Australian New Zealand Clinical Trials Registry (ANZCTR) [19] is an online register of clinical trials in

Australia and New Zealand. In 2007, the ANZCTR was recognised by the WHO ICTRP. The European Union Clinical Trials Register (EU-CTR) [20] allows users to search for protocol and results information of clinical trials conducted in the EU and the European Economic Area. The EU-CTR currently includes 43,699 clinical trials with a EudraCT protocol, of which 7251 are clinical trials involving subjects less than 18 years old, and information about 18,700 older paediatrics trials.

There are concerns that the number of ONFH patients will drastically increase due to corticosteroid treatment for COVID-19 pneumonia [1–3], and there are high expectations worldwide for regenerative medicine for ONFH treatment. In this study, clinical trials on non-traumatic ONFH were classified into six categories, including regenerative therapy. Cell therapy using CD is estimated to be the most widely used, but it is unclear what and how many clinical trials are being conducted worldwide. The results of the trials, published papers and commercialised products were also investigated. The purpose was to identify trends in clinical trials including regenerative medicine for ONFH in five major clinical trial registries: the EU-CTR, ClinicalTrials.gov, ChiCTR, UMIN-CTR and ANZCTR.

Methods

Data collection from clinical trial registries

This study is a survey of data from major clinical trial registries around the world. Clinical trials on non-traumatic ONFH were extracted from public clinical trial registry data from the EU, the U.S., China, Japan, Australia and New Zealand. We accessed the online websites of five publicly available registries and performed a word search for ‘osteonecrosis’ on 15 October 2023. From the initial search results, we excluded

diseases that were not non-traumatic ONFH, such as osteonecrosis of the jaw, osteonecrosis of the knee, OA, osteoporosis and traumatic ONFH; however, clinical trials spanning both ONFH and other diseases such as OA were incorporated. The following details were recorded: clinical trial number, study phase, objectives, interventions, study design, number of patients, organisation (sponsors, principal investigators, location), description of progress and results statement. The official names and URLs of the five clinical trial registries are as follows:

The EU registry: EU-CTR; https://www.clinicaltrialsregister.eu/ctr-search/search [20]

The U.S. registry: ClinicalTrials.gov; https://www.clinicaltrials.gov/ct2/home [15]

The Chinese registry: ChiCTR; http://www.chictr.org.cn [18]

The Japanese registry: UMIN-CTR; https://www.umin.ac.jp/ctr/index-j.htm [17]

The Australian and New Zealand registry: ANZCTR; https://www.anzctr.org.au [19]

Classification of clinical trials

The ONFH clinical trials were classified into six categories based on their purpose (Table 1): (1) surgical treatment, (2) non-drug conservative treatment, (3) conservative drug treatment, (4) therapeutic strategy, (5) diagnosis and pathogenesis and (6) regenerative therapy. Surgical treatment was subdivided into THA (including outcomes of specific implants) and joint-preserving surgery (including outcomes that validated the surgical techniques). Non-drug conservative treatment included hyperbaric oxygen therapy and extracorporeal shock waves. Conservative drug treatment included parathyroid hormone (PTH), bisphosphonates, and other drugs. Therapeutic strategy included clinical trials on the overall treatment approach for ONFH, while diagnosis and pathogenesis aimed at improving methods of diagnosing ONFH and analysing factors that affect ONFH development; these two categories differed from the other four in that

they did not include trials for drug approval. Regenerative therapy was classified into cell therapy, bone substitute, and growth factor. Cell therapy was further subdivided into bone marrow derivatives (bone marrow mononuclear cells [BMMNCs] and bone marrow cells [BMCs]), mesenchymal stem cells (MSCs) and platelet-rich plasma (PRP).

Comparison of regenerative therapy for ONFH between two periods

We analyzed the details of regenerative therapy in three time periods: from 1997 to 2006, from 2007 to 2015 and from 2016 to October 2023. Details of each cell therapy, bone substitute and growth factor, including start date, type and autograft or allograft, were recorded.

Publication of registered clinical trials on regenerative medicine

We determined whether the trial results were presented in the registry and in papers after completion. The terms ‘name of the investigators’ or/and ‘osteonecrosis’ were searched in PubMed.

Results

Number of clinical trials on ONFH

Figure 1 illustrates study enrolment. Details of the number of clinical trials are summarised in Table 2. The search for 'osteonecrosis' from five clinical trial registries yielded 408 results. Excluding non-traumatic ONFH clinical trials, we obtained 169 trials. Of the six categories, surgical treatment was the most common (62 trials; 55% related to THA outcomes), followed by regenerative therapy (37 trials, all based on CD), conservative drug therapy, diagnosis and aetiology, non-drug conservative therapy and therapeutic strategy. In conservative drug treatment, PTH was used in 2 trials,

191 bisphosphonates in 13 trials and other drugs in 12 trials. Diagnosis and aetiology were
192 found in 13 trials in the U.S., 7 in China and 1 in Japan. Non-drug conservative
193 treatment included hyperbaric oxygen therapy in the EU and the U.S., ozone therapy
194 and extracorporeal shock wave lithotripsy in China and extracorporeal shock wave
195 lithotripsy in Japan. Therapeutic strategy found in 6 trials in China, 2 of which were
196 COVID-related studies, and 2 trials in Japan.

197 ***Registry-wise data***

198 Nine clinical trials were registered in the EU-CTR, with five on regenerative medicine
199 with cell therapy, two on non-drug conservative treatment and one on bisphosphonates.
200 There were 79 clinical trials registered on ClinicalTrials.gov, with 29 (37%) on surgical
201 treatment, of which 24 (83%) were THA evaluations. There were 12 trials on
202 conservative drug treatment (bisphosphonates in 9 and other drugs in 3), 1 on non-drug
203 conservative treatment and 13 on diagnosis and aetiology. Regenerative medicine was
204 used in 24 trials (30.4%; cell therapy in 21 trials, bone substitutes in 2 and growth factor
205 in 1).

206 There were 54 clinical trials registered in the ChiCTR, of which 20 were on surgical
207 treatment (joint preservation in 16 and THA in 4), 7 on non-drug conservative
208 treatment, 8 on conservative drug treatment (bisphosphonates in one and Chinese herbal
209 medicine in six. Skin cream in one), 6 on therapeutic strategy, 7 on diagnosis and
210 aetiology and 6 on regenerative medicine (cell therapy in 3 and bone substitutes in 3).
211 These six regenerative therapy trials were parallel comparative studies; two tantalum
212 studies were also designed to compare cell therapies or another porous tantalum
213 product. One study was designed to compare 3D printed titanium CAGE and two types
214 of artificial bone.

There were 22 clinical trials registered in the UMIN-CTR, of which 10 were on surgical treatment (THA in 9 and joint preservation in 1), 2 on non-drug conservative treatment and therapeutic strategy each, 1 on diagnosis and aetiology and 5 on conservative drug therapy (PTH in 2 and other drugs in 3). There were only two trials on regenerative therapy, which were identical clinical trials in different phases using recombinant human fibroblast growth factor-2 (rhFGF-2).

Finally, five clinical trials were registered in the ANZCTR (three on bisphosphonates and two on THA). No regenerative therapy trials were registered.

Regenerative therapy for ONFH

Table 3 shows the details of regenerative therapy for ONFH. Of the 37 clinical trials, 29 used cell therapy, 5 used bone substitutes and 3 used growth factors; 27 were conducted by non-commercial organisations and 10 by commercial organisations;14 were randomised controlled trials (RCTs; 2in the EU and 12 in the U.S.) and 23 were open label; and 5 trials were in phase 1, 5 in phases 1–2, 8 in phase 2, 1 in phases 2–3, 6 in phase 3, 1 in phase 4 and 11 were not applicable.

Cell therapy

The percentage of cell therapy trials was highest in the EU (5/8, 62.5%), while the number of cell therapy trials was the largest in the U.S. (n = 21). The cell types were BMCs in 13 trials, BMMNCs in 6 trials, MSCs in 7 trials and PRP in 3 trials. The auto-BMC-derived product PREOB® (Bone Therapeutics SA, Belgium) was registered for one clinical trial in the EU and two in the U.S. PREOB® received orphan drug designation for ONFH from the European Medicines Agency in October 2007 and from the FDA in March 2008. However, in November 2018, the phase 3 PREOB® study was discontinued because, based on the interim analysis results, the Data Safety Monitoring

239 Committee determined that PREOB® is not superior to CD alone in pain scores and
240 radiological assessment and that it is unlikely that the primary endpoint would be met in
241 the final analysis [21].

242 ***Bone substitutes***

243 Bone substitutes were tested by two types of bone cement in the U.S. and two three
244 implants in China. The two types of bone cement, polymethyl methacrylate (PMMA)
245 and calcium phosphate paste, were registered in 1997 and 2006, respectively, in the U.S.
246 Two clinical trials using porous tantalum implants were registered in China.

247 ***Growth factors***

248 Only three trials used growth factors. One trial used recombinant human bone
249 morphogenic protein (rhBMP)-7 combining autologous bone marrow in the U.S., and
250 two trials in Japan used rhFGF-2 in gelatin hydrogel.

251 ***Comparison of regenerative therapy for ONFH between two periods***

252 Table 4 presents the details of regenerative therapy in two time periods: until December
253 2010 and from January 2011 to October 2023. Cell therapy changed from bone
254 marrow–derived products to cultured MSC products and PRP from 2010 to 2019.

255 ***Publication of registered clinical trials on regenerative medicine***

256 Of the five EU trials on cell therapy, four were ongoing and only one listed the results
257 and its discontinuation on the website in October 2023 [21]. Of the 21 trials on
258 regenerative therapy from the U.S., 4 were ongoing and 8 had been published [22–31].
259 Of the six trials on regenerative therapy from China, four were from 2018 or later and
260 one was listed as ongoing; the results had not yet been released. The two clinical trials
261 from Japan using growth factors had been published [32, 34]. Overall, 10 of the 37
262 regenerative therapy trials were listed as ongoing, confirming the publication of the

results of 11 trials. In an RCT of patients with stage 3 ONFH, BMC implantation was not effective in the clinical score and radiological evaluation [22]. The 10-year hip survival was better with reinjection of BMCs and BMP-7 than with CD alone [23]. For early-stage ONFH patients with sickle cell disease, BMMNC implantation with CD was reported as a safe and effective treatment at 5-year follow-up [24]. On 10-year follow-up, BMC implantation was effective in three validated clinical scores compared to CD alone [25, 26]. The change in the osteonecrotic lesion size 2 years post-implantation of adipose derived MSCs reduced on magnetic resonance imaging [27]. Implantation combining PRP, MSCs and allograft bone using CD for stage 3 ONFH patients showed good results similar to stage 1 and 2 patients [28]. After 5 years of MSC implantation, 80% of 21 ONFH patients showed no progression [29, 30]. Tracking iron-labelled BMC transplants for ONFH patients did not show negatively affected bone repair [31]. The administration of gelatin hydrogel containing rhFGF-2 had a higher survival rate on radiological assessment than on natural history in both the first-in-human [32, 33] and multi-centre [34] trials.

Discussion

Various clinical trials, including (1) surgical treatment, (2) non-drug conservative treatment, (3) conservative drug treatment, (4) therapeutic strategy, (5) diagnosis and pathogenesis and (6) regenerative therapy, have been registered from the websites of five major registries EU-CTR, ClinicalTrials.gov, ChiCTR, UMIN-CTR and ANZCTR. There were 169 clinical trials on ONFH. Of these, 37 were on regenerative medicine, including 29 on cell therapy. Surgical treatment was the most common treatment, followed by regenerative therapy. There were 9 clinical trials registered in the EU-CTR,

287 with 5 on regenerative medicine; 79 trials registered on ClinicalTrials.gov, with 24 on
288 regenerative medicine; 54 trials registered in the ChiCTR, with 6 on regenerative
289 medicine. Six herbal medicines were used for ONFH in China, not in other regions.
290 Whether osteoporosis drugs have a therapeutic effect on ONFH is controversial, and the
291 U.S. recommendations of 2015 and 2020 are insufficient [4]. The 2019 Chinese
292 guidelines on epidemiology, aetiology, pathology, imaging and diagnostic methods are
293 new [10]. The clinical trials registered from China seem to indicate substantial interest
294 in ONFH. Since approximately the year 2000, the focus of research has shifted to
295 regenerative therapy based on minimally invasive surgery modified CD in early-stage
296 ONFH for the purpose of bone regeneration and ultimately to prevent femoral head
297 collapse. Regenerative therapies have emerged, combining CD with cells, bone
298 substitutes and growth factors. Treatment guidelines and reviews are frequently updated
299 worldwide. Europe and the U.S. are leading the way in CD-based regenerative therapy,
300 while cell-based therapy is not being used in Japan [12]. The reason could be the
301 differences in treatment recommendations between Europe and the U.S., and Japan. In
302 Japan, the latest 2019 guideline gives CD a grade of 3 as strength of recommendation,
303 meaning weakly recommended [5], while the U.S. concept review of 2020 gives CD
304 and cell therapy a grade of A, meaning good evidence [4]. Therefore, Japan is lagging
305 behind other countries in cell therapy practice. Historically, BMMNC and BMC use was
306 common until 2010, and MSC and PRP use increased after 2011. Hernigou et al. [35]
307 collected bone marrow from the iliac crest and used a cell centrifuge to separate the
308 fraction containing mononuclear cells, which were injected into the osteonecrotic site;
309 8–18 years later, only 94 (17.6%) of 534 patients with pre-collapse ONFH reported
310 progression of femoral head collapse. Gangji et al. [36] also conducted a prospective

311 double-blind study of 24 hips, comparing CD alone and CD with autologous BMMNCs
312 for over 5 years. Radiological femoral head collapse was observed in 8 (72.7%) of 11
313 joints in the CD group and in 3 (23.1%) of 13 joints in the CD + BMMNC group.
314 Papakostidis et al. [37] reported that in pre-collapse ONFH, CD with transplantation of
315 autologous BMCs is clinically effective and can improve femoral head survival and
316 reduce the need for THA [37]. However, in June 2020, discontinuation of the
317 development of autologous BMC products, which had been tested for efficacy required
318 for regulatory approval in the EU and the U.S., may have had some impact [21]. Li et al.
319 [38] reported that cell therapy is considered a reliable regenerative approach for early-
320 stage ONFH and that further high-quality, large-sample, multi-centre, long-term follow-
321 up RCTs are needed for clinical application. The advantage of autologous BMMNCs is
322 that collection and transplantation can be easily completed in one step using centrifuge
323 equipment.
324 Autologous cultured cell transplantation is a two-step procedure of harvesting and
325 administration and is custom-made for individual patients. Therefore, it is impossible to
326 supply the product in large quantities, which is a barrier to cell therapy usage. Allogenic
327 cell therapy; however, can be prepared in advance and requires only one step, but
328 further validation is needed. Therefore, research in China since 2018 has shifted to PRP,
329 while in the U.S. and Europe, it has shifted to MSC-derived cell therapy. Autologous
330 cell therapy has been the mainstream so far, but in 2018 and 2020, two clinical trials
331 using allogeneic MSCs were registered from Europe and the U.S. The trials are
332 underway by exit companies for regulatory approval, and there are high expectations in
333 terms of supply and dissemination.

PMMA and calcium phosphate (bone cements) were used as bone substitutes until 2010, and porous tantalum since 2011. PMMA causes osteonecrosis due to polymerisation reactions, and its use in ONFH has been discontinued. Yu et al. [39] reported the use of an injectable calcium phosphate bone prosthesis ($CaSO_4$/$CaPO_4$ composite) in ONFH, and 19 joints in 18 patients (3/6 joints [50%] with pre-collapse ONFH and 8/13 joints [61.5%] with early collapsed ONFH) underwent THA at an average of 8.5 months post-operatively. Products on the market include Zimmer Trabecular Metal (porous tantalum; Zimmer, Warsaw, IN, USA), available in both small and large diameters for CD. Tsao et al. [40] used large-diameter rods in 113 joints of 97 patients with pre-collapse ONFH and performed THA in 19 joints (19.6%) over 4 years of follow-up. Veillette et al. [41] reported that of 48 joints in 42 patients, 16 (33.3%) experienced femoral head collapse over 4 years [41]. Floerkemeier et al. [42] reported that 13 of 23 joints (56.5%) with ONFH progression required THA after an average of 1.45 years [42]. The outcomes after combined CD and tantalum rod insertion are not considered superior to those of CD alone, and in some patients, the tantalum rod was difficult to remove during conversion to THA. Therefore, the use of porous tantalum for ONFH is decreasing, with the U.S. grading it as C, meaning poor-quality evidence [4].

BMPs are reported to be factors with ectopic osteogenic potential present in the demineralised bone matrix. BMPs are well known as bone- and cartilage-inducing factors that promote bone formation in vivo. Due to gene cloning, there are ~20 isoforms of BMPs, among which BMP-2, BMP-4, BMP-6 and BMP-7 strongly affect bone formation. A commercial medical device (InFUSE Bone Graft; Medtronic Sofamor Danek, Inc, Minneapolis, MN, USA) combining rhBMP-2 and absorbable

collagen sponge induces bone regeneration. rhBMP-7 (Putty; Stryker, Kalamazoo, MI, USA) is available for treatment of lumbar fusion and long-bone fractures [43]. FGF-2 has proliferative and angiogenic effects and has been extensively studied in vivo and in vitro. In Japan, two rhFGF-2 products were approved in 2016 for periodontal disease (Regrowth; Kaken Pharmaceuticals Co., Ltd., Tokyo, Japan) and in 2019 for tympanic membrane perforation (Retympa; Nobelpharma Co., Ltd, Tokyo, Japan) [34, 43]. Based on results from preclinical research using an experimental ONFH rabbit model, FGF-2 has been used in Japan since 2013 with gelatin hydrogel as a scaffold. In the first-in-human clinical trial with 10 patients with pre-collapse ONFH [32], rhFGF-2 was administered in CD and only 3 patients showed femoral head collapse at 5 years [33]. In phase 2, 64 patients with a large extent of ONFH had substantially less femoral head collapse compared to the natural course as an endpoint with radiological femoral head collapse [34]. However, rhFGF-2 has yet to be approved by regulatory authorities. Based on the premise that autologous cell therapy is as safe as other autologous tissues, such as autologous bone, BMMNC treatment began in the nineties, mainly in university hospitals and large hospitals. However, no global standard regenerative medicine for ONFH has emerged yet. There are several reasons. Firstly, because of autologous cell transplantation, efficacy has not been validated and clinical application has been early. Normally, safety and efficacy must be confirmed for clinical application, but clinical application has been preceded by the fact that safety is self-evident. The bone marrow of ONFH patients treated with corticosteroids has lower bone formation capacity compared with healthy subjects, which is not favourable for cell therapy. Secondly, autologous transplantation is custom-made for each patient. The use of pre-manufactured bone substitutes and growth factors will spread faster, but they are not

verified. Thirdly, although pre-collapse ONFH is the optimal indication for CD-based regenerative medicine, some clinical trials included advanced ONFH cases after femoral head collapse. Since early diagnosis and early treatment are prerequisites for regenerative medicine, improvements in diagnostic techniques and accuracy are required and the public needs to be aware of ONFH. In addition, the clinical trial design should be limited to early ONFH and RCTs should be conducted to verify efficacy. Fourthly, clinical trials mainly by universities and research institutes are not intended for approval and can only lead to regional dissemination. Fifthly, the long-term results of THA have improved and the procedure is now being performed on younger patients. However, while THA is a final option for end-stage ONFH patients, it should be avoided in young patients because of the lifelong risk of infection and dislocation, the need for revision surgery, high medical care costs, and loss to society.

This study had several limitations. Firstly, this review was based on data from only five registries in five regions. Therefore, this study did not reflect data from other regions, such as Russia, India and Africa and unpublished research. As of October 2023, 18 clinical trial registries worldwide provide clinical trials information to the ICTRP. Secondly, we could not fully investigate whether the registered clinical trials had been published. In 2017, the FDAAA required publication of results within 1 year from trial completion date. However, more than 30% of clinical trials in the U.S. [44] were not fully compliant with result registration. Due to the limited publications in many trials, the long-term effectiveness of these therapies or comparisons of outcomes between different therapies remains unclear. The accumulation of long-term follow up data will be required in future clinical studies. Thirdly, we also could not investigate whether the products had been approved by regulatory authorities or commercialised after trial.

406

407 **Conclusions**

408 Clinical trials on ONFH are in the process of validating the efficacy of CD-based cell
409 therapy for approval. The percentage of regenerative medicine using cell therapy is high
410 in the EU and the U.S. In China and Japan, the percentage of regenerative medicine is
411 low. However, although there are great expectations for regenerative medicine for
412 ONFH, no global standard regenerative therapy has been established yet.

413

414 **Expert opinion**

415 ONFH is a refractory joint disease that causes femoral head collapse, pain, limitation of
416 hip motion and gait disability. The etiology of ONFH is considered to be multifactorial
417 and is associated with several risk factors. Corticosteroid use and excessive alcohol
418 intake are most often considered two major causative factors for nontraumatic ONFH.
419 To date, the COVID-19 outbreak which began in 2019 has necessitated systemic
420 corticosteroid therapy for 18% of COVID-19 patients in China. As the incidence of
421 corticosteroid-associated ONFH after outbreak of SARS in 2003 was reported to be
422 24%, the incidence of this condition might increase rapidly after the COVID-19
423 pandemic. In clinical practice, 70–80% of patients with ONFH experience femoral head
424 collapse and most require THA. Although THA is a currently successful orthopedic
425 procedure, the main issue with ONFH is that it affects patients as young as 20 years of
426 age; ONFH is the main reason for THA in this young population. Younger patients are
427 hesitant to undergo artificial joint surgery due to its restrictions on sports activity, the
428 lifelong risks of infection and dislocation, high medical costs and potential for further
429 revision surgery. Historically, various joint-preserving surgeries such as osteotomy or

vascularized bone grafting have been performed, but the clinical outcomes have not been uniform due to the difficulty of these surgical procedures. Recently, the focus of research has shifted to regenerative therapy based on minimally invasive surgery modified CD in early-stage ONFH for the purpose of bone regeneration and ultimately to prevent femoral head collapse. Since approximately the year 2000, regenerative therapies have emerged, combining CD with cells, bone substitutes and growth factors. Treatment guidelines and reviews are frequently updated worldwide. Cell therapies using autologous cells have been performed in numerous countries given the established safety of autologous tissue transplants. The beneficial effects of cell therapy have been suggested. However, a recent concept review from the USA stated that the biological augmentation of CD has shown promising results in providing symptomatic relief and slowing the natural progression of ONFH, but more study is necessary to establish its efficacy. Regenerative medicine is considered the next treatment of interest to preserve hip joints. However, there has been limited validation for these newer regenerative therapies. Therefore, the purpose was to identify trends in clinical trials including regenerative medicine for ONFH in five major clinical trial registries: the EU-CTR, ClinicalTrials.gov, ChiCTR, UMIN-CTR and ANZCTR. This study surveyed clinical trials on regenerative medicine for ONFH. There were 37 clinical trials on regenerative medicine, including 29 on cell therapy. However, no global standard regenerative medicine for ONFH has emerged yet. There are several reasons. Firstly, because of autologous cell transplantation, efficacy has not been validated. In addition, it is difficult that the clinical trial design should be limited to early ONFH and RCTs should be conducted. The global standardisation of regenerative therapy for ONFH is still ongoing. Further high-quality studies are essential for regenerative treatment to be

adopted into general clinical practice. Regenerative therapy using cells is a simple method and is expected to be applies clinically for young patients with ONFH in future. This new treatment might have a major impact on physical activities, medical costs.

List of Abbreviations

ANZCTR **Australian New Zealand Clinical Trials Registry**

BMC **Bone marrow cells**

BG **Bone grafting**

BMMNC **Bone marrow mononuclear cells**

CD **Core decompression**

ChiCTR **Chinese Clinical Trial Registry**

FDAAA **Food and Drug Administration Amendments Act**

FGF **Fibroblast growth factor**

ICMJE **International Committee of Medical Journal Editors**

ICTRP **International Clinical Trial Registry Platform**

MSC **Mesenchymal stem cells**

ONFH **Osteonecrosis of the femoral head**

PTH **Parathyroid hormone**

PRP **Platelet-rich plasma**

RCT **Randomised controlled trials**

SARS **Severe acute respiratory syndrome**

THA **Total hip arthroplasty**

UMIN **University Hospital Medical Information Network**

WHO **World Health Organisation**

Declarations

Ethics approval and consent to participate

This study is a survey of data from five public online clinical trial registries. Therefore, no protocol or relevant ethics committee approval was required.

Availability of data and materials

Not applicable.

Declaration of interests

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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YK, TK, YO, YM and SM drafted and completed the manuscript. All of the authors read and approved the final manuscript.

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635

636 **Tables**

637 **Table 1.** Six categories of clinical trials on ONFH

Category	Content
1. Surgical treatment	THA, joint-preserving surgery different from regenerative therapy
2. Non-drug conservative treatment	Hyperbaric oxygen therapy, extracorporeal shock, etc.
3. Conservative drug treatment	PTH, bisphosphonate, others (herbal medicine, skin cream etc.)
4. Therapeutic strategy	Selection of therapeutic procedure
5. Diagnosis and pathogenesis	Search for diagnostic methods and etiology
6. Regenerative therapy	Cell (BMMNC/ BMC, MSC, PRP), bone substitute, growth factor

638 THA, total hip arthroplasty; PTH, parathyroid hormone; BMMNC, bone marrow
639 mononuclear cell; BMC, bone marrow cell; MSC, mesenchymal stem cell; ONFH,
640 osteonecrosis of the femoral head; PRP, platelet-rich plasma.

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642 **Table 2.** Total number and categorical summaries of clinical trials

	EU	U.S.	China	Japan	Australia–NZ	Total
	n **(%)**	***n*** **(%)**	***n*** **(%)**	***n*** **(%)**	***n*** **(%)**	***n*** **(%)**
Total number of clinical trials for ONFH	9 (100%)	79 (100%)	54 (100%)	22 (100%)	5 (100%)	169 (100%)
1. Surgical treatment	1 (11.1%)	29 (36.7%)	20 (37.0%)	10 (45.5%)	2 (40%)	62 (36.7%)
THA	0	24	4	9	2	39
Joint-preserving surgery	1*	5	16	1	0	23
2. Non-drug conservative treatment	2 (22.2%)	1 (1.3%)	7 (13.0%)	2 (9.1%)	0 (0%)	12 (7.1%)
3. Conservative drug treatment	1 (11.1%)	12 (15.2%)	8 (14.8%)	5 (22.7%)	3 (60%)	29 (17.2%)
Bisphosphonate	1	9	1	0	3	14
PTH	0	0	0	2	0	2
Others	0	3	7	3	0	13
4. Therapeutic strategy	0 (0%)	0 (0%)	6 (11.1%)	2 (9.1%)	0 (0%)	8 (4.7%)
5. Diagnosis and pathogenesis	0 (0%)	13 (16.5%)	7 (13.0%)	1 (4.5%)	0 (0%)	21 (12.4%)
6. Regenerative therapy	5 (55.6%)	24 (30.4%)	6 (11.1%)	2 (9.1%)	0 (0%)	37 (21.9%)
Cell therapy	5	21	3	0	0	29
Bone substitute	0	2**	3***	0	0	5
Growth factor	0	1†	0	2‡	0	3

The five joint-preserving surgeries were classified separately from regenerative therapy. The EU and the U.S. have a higher-than-average share of regenerative therapy. China and Japan had clinical trials registered in all six categories. The others category under conservative drug treatment mainly included herbal medicines in China and statin and lansoprazole in Japan.

*This study used joint-preserving surgery and drug treatment.

**One study used cell therapy and bone substitute.

***Both clinical trials were tested with tantalum implants with CD.

†This study used bone marrow and rhBMP-7.

‡These two similar studies used rhFGF-2 in gelatin hydrogel with different phases.

EU, European Union; NZ, New Zealand; ONFH, osteonecrosis of the femoral head; CD, core decompression; THA, total hip arthroplasty; PTH, parathyroid hormone; rhBMP-7, recombinant human bone morphogenic protein-7; rhFGF-2, recombinant human fibroblast growth factor-2.

Table 3. Lists of registered regenerative clinical trials for ONFH

Start year	Trial number	Phase	Study design	Content	Autograft/allograft	No. of patients	Organisation	Status	Reference
EU									
2006	2006-001286-42	3	RCT	BMC	Autograft	15	Company (U.S.)	Ongoing	NA
2009	2009-012929-11	3	RCT	PREOB® (cultured BMC)	Autograft	68	Company (DE)	Discontinued	21
2011	2011-005258-70	2	Open label	MSC	Autograft	10	University (ES)	Ongoing	NA
2014	2012-002010-39	2	Open label	MSC	Autograft	6	University (ES)	Ongoing	NA
2018	2018-000886-35	2	Open label	MSC	Autograft	7	Company (ES)	Ongoing	NA
U.S.									
1997	NCT04233125	1, 2	RCT	PMMA	-	37	University (U.S.)	Completed	NA
1999	NCT00821470	1	Open label	BMMNC	Autograft	21	University (BE)	Completed	NA
2003	NCT02890537	2	RCT	PREOB® (cultured BMC)	Autograft	82	Company (DE)	Completed	NA
2004	NCT01544712	NA	RCT	BMC	Autograft	50	University (BE)	Completed	22
2005	NCT02655120	NA	RCT	BMC with rhBMP-7	Autograft	41	University (FR)	Completed	23

2006	NCT02448121	1, 2	Open label	MSC	Autograft	100	University (BR)	Completed	24
2006	NCT01892514	2	Open label	Calcium phosphate with cellulose gel	-	12	Company (FR)	Completed	NA
2007	NCT00505219	3	RCT	BMC + DBM	Autograft	11	Company (U.S.)	Completed	NA
2009	NCT01198080	1	Open label	BM derived CD133 + cells	Autograft	10	University (IR)	Completed	NA*
2009	NCT00813267	1	Open label	BMMNC	Autograft	15	University (CN)	Completed	NA*
2009	NCT01613612	2, 3	RCT	BMC	Autograft	60	Hospital (CN)	Completed	25, 26
2011	NCT01529008	3	RCT	PREOB® (cultured BMC)	Autograft	55	Company (DE)	Completed	NA
2012	NCT02721940	NA	RCT	BMMNC, platelets, zoledronic acid	Autograft	100	Hospital (CN)	Completed	NA*
2012	NCT0170092	2	Open label	MSC	Autograft	3	Institute (ES)	Completed	NA
2012	NCT01643655	NA	Open label	Adipose tissue derived MSC	Autograft	15	Hospital (KR)	Completed	27
2013	NCT01892514	3	RCT	BMC, platelet-rich fibrin, DBM	Autograft	104	University (IT)	Completed	28
2014	NCT02065167	2	Open label	MSC	Autograft	26	University (FR)	Completed	29, 30
2015	NCT02893293	4	Open label	Iron-labelled BMC	Autograft	20	University (U.S.)	Completed	31

2015	NCT01605383	1, 2	RCT	MSC with allogenic bone	Autograft	23	Institute (ES)	Completed	NA*
2017	NCT03269409	1	RCT	Adipose derived regenerative cells	Autograft	25	University (U.S.)	Ongoing	NA*
2017	NCT03787329	NA	Open label	BMC	Autograft	40	Company (TW)	Completed	NA
2020	NCT03180463	1, 2	RCT	Human umbilical cord derived MSC	Allograft	30	Company (CN)	Ongoing	NA
2023	NCT05706909	NA	Open label	BMC and Genex® bone graft substitute	Autograft	20	Clinic (U.S.)	Ongoing	NA
2023	NCT05982054	NA	Open label	MSC	Autograft	10	Institute (Iraq)	Ongoing	NA
China									
2012	12002091	1	Pararell	Porous tantalum with MSC	-	20 30	Hospital (CN)	NA	NA
2018	1800015182	3	Pararell	Comparison of two types of porous tantalum rods	-	20 20	Company (CN)	NA	NA
2018	1800020319	NA	Pararell	PRP	Autograft	60, 60	University (CN)	NA	NA

2019	1900023601	NA	Pararell	Comparison of PRP and shockwave therapy	Autograft	28, 28	Hospital (CN)	NA	NA
2020	2000037854	NA	Pararell	PRP	Autograft	20, 50	Hospital (CN)	Ongoing	NA
2022	2200062816	NA	Pararell	3D printed titanium CAGE and two types of artificial bone	-	300	Hospital (CN)	Ongoing	NA
Japan									
2012	UMIN000009250	1,2	Open label	rhFGF-2 with gelatin hydrogel	-	10	University (JP)	Completed	32, 33
2015	UMIN000020340	2	Open label	rhFGF-2 with gelatin hydrogel	-	64	University (JP)	Completed	34

668 EU, European Union; RCT, randomised controlled trial; BMC, bone marrow cell; MSC, mesenchymal stem cell; ONFH, osteonecrosis of
669 the femoral head; PMMA, polymethyl methacrylate; BMMNC, bone marrow mononuclear cell; BMP, bone morphogenic protein; DBM,
670 demineralised bone matrix; PRP, platelet-rich plasma; FGF, fibroblast growth factor; DE, Germany; ES, Spain; BE, Belgium; FR, France;
671 BR, Brazil; IR, Iran; CN, China; KR, Korea; IT, Italy; TW, Taiwan; JP, Japan; NA, not applicable.
672 *An article written by an investigator and similar in content to the clinical trial data but not mentioned in this paper.

673 **Table 4.** Comparison of regenerative therapy for ONFH by age

1997-2006		2007-2015		2016- October 2023		Total
Cell therapy	5	Cell therapy	15	Cell therapy	8	28
BMMNC/ BMC	1/ 3	BMMNC/ BMC	2/ 7	BMMNC/ BMC	0/ 1	
MSC	1	MSC	6	MSC	4	
				PRP	3	
Cell therapy	5	Cell therapy	15	Cell therapy	8	
Autograft/ allograft	5/ 0	Autograft/ allograft	15/ 0	Autograft/ allograft	6/ 2	
Bone substitute	2	Bone substitute	1	Bone substitute	3	6
PMMA	1	Porous tantalum†	1	Porous tantalum	1	
Calcium phosphate	1			Calcium phosphate*	1	
				3D-printing Ti cage	1	
Growth factor	1	Growth factor	1	Growth factor	1	3
BMP-7*	1	FGF-2	1	FGF-2	1	

674 ONFH, osteonecrosis of the femoral head; BMMNC, bone marrow mononuclear cell;
675 BMC, bone marrow cell; MSC, mesenchymal stem cell; PRP, platelet-rich plasma;
676 PMMA, polymethyl methacrylate; BMP, bone morphogenic protein; FGF, fibroblast
677 growth factor. * Combination with BMC. † Combination with MSC.

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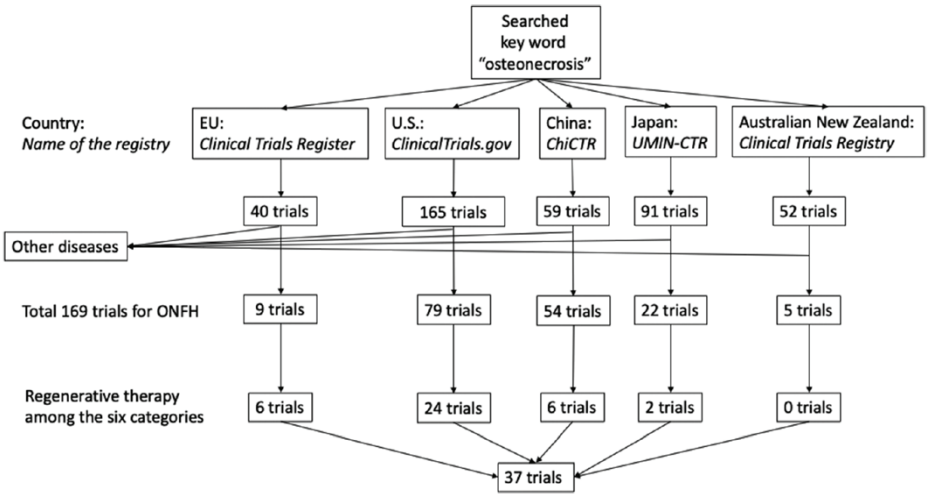
686 **Figure Legends**

687 **Figure 1. Diagram of analysis targets according to eligibility criteria from five**
688 **public clinical trial registries.**

689 Diseases that differed from ONFH were excluded from analysis. Clinical trials for
690 ONFH were categorised (Table 1) and regenerative therapies identified. EU, European
691 Union; ONFH, osteonecrosis of the femoral head.



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