Perspective on Intra-articular Injection Cell Therapy for Osteoarthritis Treatment

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Abstract

BACKGROUND: Osteoarthritis (OA), the most common arthritis, is one of the most frequently encountered orthopaedic conditions. As a small number of large joints such as knee and hip are affected in OA, OA is an ideal target for local therapy. Although corticosteroid and hyaluronic acid have been traditionally used for joints through intra-articular (IA) injection, IA injection also provides a minimally invasive route to apply cell therapy to treat OA. IA cell therapy has drawn attention because it may provide regeneration of articular cartilage in addition to palliative anti-inflammatory effects.

METHODS: Current progress of IA injection therapy and the author's perspective on this issue are described narratively.

RESULTS: It is too premature to have any conclusion on the eventual efficacy of IA cell therapy concerning regeneration of articular cartilage based on current data. Prospective radiological and histological data from larger numbers of patients are needed to prove cost effectiveness of IA cell therapy.

CONCLUSIONS: Expanding research in this field will produce further evidences to provide guidance on the eventual effectiveness of IA cell therapy in the future.

Keywords Cell therapy · Intra-articular injection · Cartilage regeneration · Osteoarthritis treatment

1 Osteoarthritis and articular cartilage

Osteoarthritis (OA) is the most common arthritis, which is also known as degenerative joint disease or degenerative arthritis. OA is a chronic disease characterized by the breakdown and ensuing loss of articular cartilage. While posttraumatic OA resulting from damaged articular cartilage (AC) has definite etiology and pathophysiological process, OA is primarily a multi-factorial, probably systemic disease. OA is accompanied by progressive focal AC degeneration, synovial inflammation, formation of osteophyte, subchondral sclerosis, and hypertrophy of the joint

capsule [1]. While the exact cause of OA is unknown, aging, hereditary, developmental and metabolic factors, and mechanical deficits are considered to be contributing factors.

AC is an avascular tissue with very limited self-regeneration potential. Such limitation leads to progressive joint destruction with accompanying pain and disability. A lot of efforts has been devoted to regenerate AC or at least arrest the progression of joint destruction. Cell therapy pioneered by autologous chondrocyte implantation (ACI) followed by stem cell therapy has been applied to patients with various success. Application of cell therapy starts with open surgeries that are invasive. As patients prefer less invasive treatment, cell therapy through arthroscopic surgery or intra-articular injection has been investigated [2].

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2 Rationale for intra-articular injection therapy in osteoarthritis and currently used substances

As OA generally affects a small number of joints intra-articular (IA) injection can be a very useful choice to treat OA [3]. IA therapeutics has advantages of direct targeting, thus avoiding systemic side effects. As of now, glucocorticoids and sodium hyaluronate (HA) are two approved substance classes that are broadly used for IA OA treatment.

Corticosteroids were the first substances used to provide appreciable symptomatic treatment of synovitis and effusion in knee OA patients [4]. Corticosteroids can inhibit prostaglandin synthesis and reduce the activity of collagenase and other matrix metalloproteinases [5]. IA injections of corticosteroid also decrease the production of inflammatory cytokines such as interleukin (IL)-1 and tumor necrosis factor alpha [6]. HA is another IA injection substance frequently used for OA treatment. The rationale for using HA started from the idea of restoring the viscoelasticity of synovial fluid. Injected HA can supplement the flow of synovial fluid, regulate endogenous HA synthesis, and inhibit its degradation [7]. Its duration of action varies dependent on the molecular weight of HA. Higher molecular weight HA generally offers higher and longer-lasting analgesia [8]. As the duration of action for either corticosteroid or HA in the longest does not last for months, both drugs require frequent injection. Also, since neither glucocorticoid nor HA offers cartilage regeneration, IA therapeutics that can provide structural improvement for AC cartilage and pain relief are desired. Kartogenin is a newly found substance that can induce chondrogenesis from mesenchymal stem cells (MSCs) [9]. The author's lab has developed kartogenin-polyethylene glycol micelle conjugated HA that can enhance chondrogenic potential and arrest progression of OA in surgically-induced OA rat model (Fig. 1) [10].

3 Cell therapeutics for IA injection in OA

Cell injection therapy in OA was originally proposed to promote healing of AC by engraftment and differentiation of administered cells into matrix-producing chondrocytes. Candidate cells can be naïve or modified chondrocytes and stem cells. While most researches on IA cell therapy have been performed using MSCs, IA cell therapeutics based on transforming growth factor (TGF)- β transfected chondrocytes (Invossa®) have been developed and now available on the market in Korea.

The desired mode of cell therapy in OA is engraftment of injected cells on the chondral defect and direct

chondrogenic differentiation [11, 12]. However, IA injected cells usually perish rapidly in joint cavity [13]. Injected cells are undetectable at 14–50 days post-infusion [14]. Rather, injected exogenous cells can stimulate the proliferation and anabolic activity of articular chondrocytes or the recruitment and chondrogenic differentiation of endogenous progenitor cells [13, 15, 16] by secreting paracrine factors or through direct cell–cell interactions. Secreted factors can act on both articular chondrocyte and synovium to control anabolic and catabolic pathways [17, 18]. Secreted immune-modulatory and anti-inflammatory factors explain great part of paracrine action of MSCs. MSCs can reverse macrophage polarization from a pro-inflammatory (M1) phenotype to an anti-inflammatory (M2) phenotype [19]. Subsidence of inflammation could result in less neurogenic pain and general down-regulation of pain pathways. These properties of MSCs may benefit OA involving inflammatory components [20].

Although major therapeutic effects of IA injected cells come from those transient paracrine actions, their *in vivo* survival and engraftment possibly improve clinical outcomes. This can be more appealing in OA in which the presence of durable tissue regenerated from MSC engraftment and differentiation is quite pertinent and desirable for long-term good results [20].

In a previous study, we have shown that MSCs or induced pluripotent stem cells which were implanted into chondral defect as pellets or implanted in alginate gel can persist beyond three months (Fig. 2) [21]. A comparison of arthroscopic outcomes after MSC therapy done by injection or implantation showed that the implantation method resulted in significantly greater improvements than the injection method [22]. These findings indicate that measures to immobilize MSCs at cartilage defects may be necessary to avoid massive cell death if AC regeneration from the differentiation of administered MSC and structural improvement needs to be achieved.

Human adipose stem cells (hASCs) are known to prolong the survival of ASCs and enhance anti-inflammatory effect [23]. The author has also tested if injection of hASCs in spheroid form could prolong the survival of ASCs in the joint cavity of immunosuppressed rats. When injected into knee joints of rats, MSCs in spheroid form showed enhanced survival compared to MSCs in saline suspension until 21 days after injection while hASCs in either form were undetectable at 28 days after injection, suggesting that injection of spheroidal form of MSCs could not improve long-term survival and engraftment within the joint compared to suspension form.

Fig. 1 Construction of PEG/KGN micelles-covalently integrated HA hydrogels (HA/PEG/KGN). Synthetic route (**A**) and schematic illustration (**B**) of HA/PEG/KGN (KGN, kartogenin; PEG, polyethylene glycol; OH-PEG-NH₂, heterobifunctional amine-PEG-

hydroxyl; DCC, dicyclohexylcarbodiimide; DMAP, dimethylaminopyridine; EDA, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide; SA, succinic anhydride; EDA, ethylenediamine). Reproduced with permission from Kang et al. [10]

4 Points to consider in IA cell therapy for OA

While most preceding studies have used autologous cells, allogeneic cells which can be used off-the-shelf provides great advantages regarding clinical applications in outpatient setting [24]. The prominent merit of using allogeneic cells is the lower cost of therapy that could facilitate commercialization [25]. It should be noted that stem cells derived from different tissues show significant differences in multi-potentialities and functions, even those with the same tissue type but from different anatomical sites [26]. Bone marrow (BM) and adipose tissue yield different amounts of adult stem cells per volume of obtained tissues. ASCs have much greater cell yield, reaching 10% of whole isolated nucleated cells while only 0.001–0.01% of

nucleated cells in bone marrow aspirate are BM MSCs [27, 28]. ASCs also show greater proliferative potential than BM MSCs [29]. MSC dose is also an important variable for effective OA treatment. Optimal MSC dose may differ from one individual donor/recipient to another depending on passage numbers cell and expansion methods. Nevertheless, as of now, infusion of $> 1 \times 10^7$ MSCs is reported to be necessary for significant repair in humans [30, 31]. The presence of optimal dose has also been identified in the author's caprine study. Our group has developed SOX-6, 9-transfected ASC therapeutics and subsequently injected them into knee joints of goats who had developed surgically-induced OA by preceding medial meniscectomy 2 months before injection. Three concentrations [mid-dose (6×10^6 cells corresponding to 1×10^7

Fig. 2 *In vivo* repair of osteochondral defects using chondro-induced pluripotent stem cells as pellets or incorporated in alginate gel. Gross appearance of the defects: yellow dots outline the defect

margin (A), IHC for human antigen shows persistent survival of implanted cells: positive cells are bright green (B). Reproduced with permission from Ko et al. [21]

cells in humans), low dose (1/3 of mid-dose), high dose (3 times high dose)] were used in single injection (Fig. 3). The best result in cartilage regeneration was obtained from the mid-dose while high dose was associated with

increased inflammatory cytokine and progression of OA (Fig. 4) [32].

Stage of disease progression should also be taken into consideration for cell therapy in OA. Patients with early to mid-advanced OA (Kellgren–Lawrence grade 2–3) are

Fig. 3 *In vivo* study to test the effectiveness of Sox 6,9-transfected adipose stem cells (SOX-6,9 ASCs) in the surgically-induced osteoarthritis model in goats

Fig. 4 Gross findings of AC and inflammatory cytokines levels of the synovial fluids in OA-induced goats. **A** As representative gross image of each of the five treatment groups; osteoarthritic lesions are denoted in red boxes. $n = 6$ per each group. **B** Macroscopic scores of femoral and tibial articular surfaces. The OARS scoring system takes into account the macroscopic findings of cartilage (score: 0–16) and osteophytes (score: 0–12) at 4 sites per knee joint. **C** interleukin(IL)-1 β and tumor necrosis factor (TNF)- α levels were analyzed in joint

fluids at injection sites in OA-induced knees and normal knees by enzyme-linked immunosorbent assay. Negative controls were injected with vehicle (phosphate buffered saline), the hASC group was injected with 0.6×10^7 naïve hASCs, the low-dose group was injected with 0.18×10^7 SOX-6,9 ASCs, the mid-dose group was injected with 0.6×10^7 SOX-6,9 ASCs, and the high-dose group was injected with 1.8×10^7 SOX-6,9 ASCs. $*p < 0.05$ versus negative control. Reproduced with permission from Ko et al. [32]

considered to be possible candidates for MSC therapy [33]. Clinical improvements have declined at 6 months after MSC treatment in KL 4 OA patients [25]. Patients with larger lesions also exhibited significantly inferior outcomes. From one study, patient age had high prognostic value. MSC treatment was effective in patients aged < 60 years old [34].

5 Future perspective for cell therapy in the treatment of OA

In vivo animal studies invariably precede clinical application to provide evidence for effectiveness and safety of cell therapeutics. However, results of animal studies should be interpreted with caution because results may not always be reproducible in humans. While regeneration of cartilage defects is a tough task even in otherwise healthy AC, regeneration of AC is a daunting task in the inflammatory

environment of OA. After obtaining encouraging results from *in vivo* implantation of stem cells in animal models of OA, clinical applications to OA patients ranging from intermittent case reports of stem cell injection to large clinical trials to treat OA have been reported. The safety issue in IA injections of MSC has been sufficiently proved in both autologous and allogeneic MSCs. However, considering the cost and easy availability, allogeneic MSCs comprising ASCs and umbilical cord MSCs may probably become important cell sources in coming years. Dose of IA MSCs should be optimized because the dosage is related to the cost of treatment and higher dose may not always produce the best result. Multiple small doses should be probed to confirm if they could lead to better clinical result than one large dose [20].

Although symptomatic relief has been reported in most studies, hyaline AC regeneration has rarely been observed. Based on findings of animal studies, it is believed that therapeutic effects of MSCs are from paracrine

mechanisms rather than from direct incorporation into AC and producing ECM in situ. Survival and engraftment of MSCs may result in structural change in OA cartilage. Additional measures such as cell encapsulation, spheroid, or immobilization of cells may be used for the long-term survival of MSCs *in vivo* [20, 35].

The cell injection therapy to treat OA has rapidly been in use without high-quality supporting evidence. While costs of those treatments are much higher than those of conventional treatment, there is a wide difference between published evidences and marketing claims [36]. Based on current data, it is too premature to draw any conclusion on the eventual efficacy of IA cell therapy concerning AC regeneration. Prospective radiological and histological data from larger numbers of patients are needed to prove cost effectiveness of IA cell therapy. Expanding research in this field will produce further evidences to provide guidance on this issue in the future.

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Compliance with ethical standards

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

Ethical statement There are no animal experiments carried out for this article.

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