Future Trends for Unicompartmental Arthritis of the Knee: Injectables & Stem Cells

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KEYWORDS

• Arthritis • Knee arthritis • Injectable arthritis treatment • Osteoarthritis • Hyaluronic acid • Stem cell

KEY POINTS

- Intra-articular corticosteroids and hyaluronic acid injections have a role in the treatment of early arthritis of the knee.
- Platelet-rich plasma (PRP) injections alone do not promote cartilage repair.
- The role of PRP injections in early knee osteoarthritis and focal cartilage lesions still needs to be better understood.
- Ultimately, combinations of various injectable materials may be useful in treating early knee osteoarthritis.
- Stem cell therapy has potential as either an isolated approach or combined with different surgical procedures.
- Gene therapy is a possibility but probably will not be available in the near future.

INTRODUCTION

Arthritis is one of the most frequent musculoskeletal problems, causing pain, disability, and a significant economic burden. In terms of prevalence, as life expectancy increases, arthritis prevalence will also increase.[1,2] There are estimates that osteoarthritis (OA) may become the fourth-highest impact condition in women and the eighth-most important condition in men in the developed world.[3]

There is no consensus about the best treatment option for early knee arthritis. Nonsurgical options include oral medications, injections, orthoses, physiotherapy, and lifestyle modification.[4,5] The main surgical options for arthritis of the knee after failure of a nonsurgical therapy include arthroscopic surgical procedures, cartilage repair

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or transplantation, realignment osteotomies, unicompartmental arthroplasties, or total knee arthroplasties.[4,5]

One of the main issues concerning early knee OA is that there are currently no treatment options that are able to completely revert the cartilage degenerative process. Ideally, the goal of nonsurgical treatments is to retard or stop the degenerative process. Despite the presence of unicompartmental arthritis, many patients still choose to participate in high-impact activities that can result in joint discomfort and pain. As a result, there has been a large effort to develop injectable treatments that relieve symptoms and delay the progression of early OA.

Cartilage focal lesions are also common in the adult population and may progress to arthritis.[6,7] Various knee disorders, including anterior cruciate ligament (ACL) tears,[8,9] meniscal tears and previous meniscectomies,[7] disruption of the subchondral bone,[10,11] and limb malalignment,[12] may lead to the development of cartilage lesions or progression to arthritis. Early treatment of focal cartilage lesions and early knee arthritis may be a possible approach to prevent progression of knee OA.[6,7,13–15]

In this article, we discuss current nonsurgical injectable treatment options, as well as future trends for cartilage lesions and early arthritis of the knee. We also cover some potential treatments for knee OA, including stem cell and gene therapies.[16,17]

CURRENT TREATMENT OPTIONS

Corticosteroid Injections

Corticosteroid injections have been performed in the treatment of knee OA for decades.[18,19] Recent systematic reviews have discussed the efficacy of corticosteroids compared with placebo. Similarly, recent studies have compared corticosteroids with other injectable treatment options, such as platelet-rich plasma (PRP) or hyaluronic acid (HA).[20] Corticosteroid injections may be performed alone, combined with other medications, or after knee arthroscopies.[16,21] The exact mechanism of the therapeutic effect of corticosteroids in knee OA is still unclear; however, it is believed to be related to the anti-inflammatory effect of the drug.[20] The short-term benefits of intra-articular corticosteroid injections are well established. The administration of steroid injections either alone or combined with local anesthetics has been shown to be a viable short-term option and is universally accepted in clinical practice as such.[22] The long-term benefits have not been confirmed and chronic use may lead to progressive cartilage degeneration. Maricar and colleagues[20] recently published a systematic review regarding intra-articular corticosteroid injection and predictors in knee OA. Within 696 publications, only 11 matched their inclusion criteria, but only 2 trials had a primary aim to determine predictors of response to corticosteroids. The investigators could not conclusively identify any predictors of response to intra-articular use of corticosteroids in knee OA, but they reported that synovitis and knee effusion may have some correlation with clinical improvement.[20]

Autologous-Conditioned Serum

Cytokines play an important role in the mechanism of OA. Interleukin-1 (IL-1) is known as one of the most important catabolic cytokines in the cartilage breakage process. The human body naturally produces an IL-1 receptor antagonist (IL-1ra), which is believed to have the potential to limit the intra-articular effects of the catabolic cytokine IL-1. Autologous-conditioned serum is generated by incubation of venous blood with glass beads.[23,24] After incubation for 24 hours at 37°C, the blood is recovered and centrifuged. Blood monocytes are a major natural source of IL-1ra and their production of IL-1ra is greatly stimulated by culture on immunoglobulin G–coated plates.

Woodell-May and colleagues[25] reported that the autologous protein solution (APS) contained both anabolic (basic fibroblast growth factor [bFGF], transforming growth factor [TGF]-β1, TGF-β2, epidermal growth factor [EGF], insulinlike growth factor [IGF]-1, platelet-derived growth factor [PDGF]-AB, PDGF-BB, and vascular endothelial growth factor [VEGF]) and anti-inflammatory (IL-1ra, sTNF-R1, sTNF-RII, IL-4, IL-10, IL- 13, and interferon-γ [IFNγ]) cytokines and that the combination of these cytokines is a potential candidate for treatment of OA. There are several animal studies evaluating the effect of autologous-conditioned serum; however, there are few clinical trials describing its efficacy. Baltzer and colleagues[26] performed a double-blinded randomized clinical trial comparing autologous conditioned serum (ACS) with hyaluronan and with saline. In this clinical trial, they enrolled 367 patients and found that ACS provided better pain relief and functional score (Western Ontario and McMaster Universities Osteoarthritis Index [WOMAC]) outcomes at 26 weeks of follow-up.

PRP Injections

PRP injections are considered a potential treatment option to improve joint function and decrease inflammatory mediator expression by delivering platelet-derived cytokines and growth factors to the affected area. IGF, especially IGF-1, is considered one of the main anabolic growth factors for articular cartilage.[27] IGF stimulates synthesis of integrins, type-II collagen, and proteoglycans; stimulates chondrocyte adhesion; improves tissue integration; and inhibits matrix degradation.[27,28] PDGF increases chondrocyte proliferation, but it seems to have more influence on meniscal cells than articular cartilage.[27,29] TGF-β1 is 1 of the 3 isoforms of TGF-β, and has its effects on chondrocytes and cartilage synthesis.[30] However, the mechanism of action of TGF-β1 is not completely understood, as it seems that there are significant differences between in vitro and in vivo behaviors. Also, in vivo TGF-β1 is released within the initial few days postinjury, compared with a long-lasting delivery of IGF-1. Some in vitro studies described that TGF-β1 may antagonize IGF-1 on glycosaminoglycan (GAG) synthesis when applied concomitantly.[30,31] PRP may modulate the function of human osteoarthritic chondrocytes by inhibiting the action of inflammatory cytokines, such as IL-1 and nuclear factor (NF)-kB.[32,33]

Clinical studies have demonstrated that PRP injections may decrease knee pain in patients with knee OA.[34] PRP may influence pain by inhibiting the action of inflammatory cytokines such as IL-1 and NF-kB. Patel and colleagues[34] compared leukocyte-free PRP and placebo injections in the treatment of patients with Ahlback grade 1 or 2 OA without significant deformity and observed improvement in pain scores at a minimum of 6-month follow-up with either single or double PRP injections. Spakova and colleagues[35] described better results with the use of PRP compared with HA injections at both 3-month and 6-month follow-up. Kon and colleagues[36,37] showed that pain scores improved with the use of PRP injections in arthritic joints. The results were stable from the end of the 3-injection cycle up to 6 months, but worsened at the 1-year[38] and 24-month[37] evaluations. The investigators described a trend for favorable results with PRP in patients with low-grade articular degeneration (Kellgren-Lawrence score up to 2).[39] On the other hand, a current systematic review performed by Sheth and colleagues[40] concluded that the evidence for the use of PRP knee injections is equivocal, as the literature still lacks evidence to support it. Halpern and colleagues[41] evaluated magnetic resonance images (MRIs) of the knee at baseline, 1 week, and 1, 3, 6, and 12 months after PRP injection in patients with OA. Pain scores significantly decreased, and functional and clinical scores increased at 6 months and 1 year from baseline. Qualitative MRIs demonstrated no change in at least 73% of cases at 1 year.

Hyaluronic Acid Injections

Knee arthritis may reduce the concentration of HA in the synovial fluid. HA is produced by type B synoviocytes and synovial fibroblasts. It is secreted into the joint where it acts as a lubricant, shock absorber, extracellular matrix scaffold, and chondroprotective milieu facilitating chondrocyte nutrition.[42] Viscosupplementation involves intra-articular injection of a viscoelastic mucopolysaccharide component of synovial fluid (HA) after aspiration of any existing joint effusion.[43] HA is a high-molecular-weight glycosaminoglycan that consists of a repeating sequence of disaccharide units composed of N-acetyl glucosamine and glucuronic acid.[42,43] Initially, the idea of HA injection was to reestablish the normal synovial fluid viscoelastic properties. This initial hypothesis of how HA injection would act in OA joints has not been fully proven at this time, and we still do not understand the mechanism of action of HA injections.[32,44,45]

There is still some controversy about the clinical efficacy of HA viscosupplementation in the treatment of knee OA.[46] Rutjes and colleagues[47] recently published a systematic review analyzing articles from the MEDLINE (1996–2012), EMBASE (1980–2012), and Cochrane Center Register of Controlled Trials (1970–2012) databases. Their data included 89 trials involving 12,667 adults. The investigators described that 71 trials (9617 patients) showed that viscosupplementation moderately reduced pain and 18 trials showed a clinically irrelevant effect size.

FUTURE TRENDS

There is a great effort toward developing less-invasive and more "regenerative" approaches in the treatment of cartilage lesions and OA. For advanced arthritis, it seems to be more difficult to reverse the established cartilage degeneration. In the case of focal cartilage lesions and early arthritis, new approaches may be able to repair or even regenerate functional tissue, as well as slow the progression of OA. Even though we are focusing our discussion on injectables and stem cells in this article, we certainly need to emphasize that combining surgical correction of predisposing factors, such as mechanical malalignment, knee instability, or meniscus deficiency, is probably equal or more important to the treatments discussed here.

Corticosteroids

There has been very little research into creating new or modifying current corticosteroid intra-articular injections. Developing a sustained delivery of the drug into the joint is one research area. Combining corticosteroid injections with other therapies may also be another trend to its future use. Kinase inhibitors, such as p38 inhibitors, may help to improve corticosteroid effects.[48,49] To our knowledge, there is one private company performing preclinical, phase1, and phase 2 trials with new products for knee OA involving p38 inhibition, sustained effect corticosteroids, and tyrosine kinase A (TrkA) inhibitors.[50]

Lubricants and Viscosupplementation

HA formulations currently available for clinical use are quite varied, differing in molecular weight, method of production, and possibly half-life in the joint.[42] To increase the HA half-life in the joint, different cross-linking procedures are being researched. Cross-linking is a process in which the individual chains of HA are chemically bound (or "cross-linked") together, creating a more viscous substance, transforming it from a liquid into a "gel." The firmness of the gel depends on the degree of cross-linking.[51] The body metabolizes cross-linked HA slower than the non–cross linked, which may result in a longer-lasting effect in the knee joint.

Developments in the research of HA cross-linkage have resulted in highly viscoelastic materials that may be capable of preparation in a mixture of relevant growth hormones or anti-inflammatory drugs.[52,53]

New synthetic lubricants that mimic natural joint synovial fluid substances are also being studied. Lubricin (also known as superficial zone protein) is one of the primary lubricating substances in diarthrodial joints, being responsible for the lubrication of pressurized cartilage. It is mucinous glycoprotein produced by synovial fibroblasts and superficial zone articular chondrocytes. Lubricin expression is downregulated by proinflammatory cytokines, such as IL-1 and tumor necrosis factor (TNF)-alpha and upregulated by TGF-β and bone morphogenic protein (BMP)-7.[54,55] Some OA animal-model studies have demonstrated that synthetic lubricin provides a chondroprotective effect,[56] which may be more effective than HA injections.[57]

Growth Factor–Related Injections

A greater understanding of the cytokine cascades associated with OA and OA progression may lead to the development of new biologic injections. Current knowledge supports that IL-1 beta is the main cytokine in the degenerative arthritis process, and research on IL-1ra is a promising area. Substances such as IGF-1,[27,58] TGF-β, FGF-18,[59] as well as anti-inflammatory cytokines such as IL-4 and IL-10,[60] PDGF,[27] and adrenomedullin,[61] may play a role in the development of new therapies. IGF-1 is a pro-anabolic cytokine to chondrocytes, stimulating matrix deposition and, to a lesser extent, cell proliferation.

Most studies are in the preclinical phase, consisting mainly of small animal research, which may lead to clinical studies in the near future. For example, Van Meegeren and colleagues[60] demonstrated in a mouse model that a single intra-articular injection of IL-4 plus IL-10 directly after a single joint bleed limits cartilage degeneration over time. Yorimitsu and colleagues[62] demonstrated that IL-4 might promote a chondroprotective response to mechanical stress-induced cartilage destruction in OA rat models. Although some of the potential benefits of cytokine or cytokine-antagonist injections have been shown in animal studies, clinical studies concerning long-term safety of biotherapy injections is mandatory, as exposing patients to serious side effects is not acceptable in a benign disease such as OA.[63]

Inhibition of the degradative effects of matrix metalloproteinases (MMPs) to prevent cartilage and joint destruction may become another future treatment option for early OA. The family of proteolytic enzymes responsible for OA cartilage matrix digestion is the MMPs.[64] Collagenases, particularly collagenase-1 (MMP-1) and collagenase-3 (MMP-13), are involved in type II collagen degradation. Stromelysin-1 (MMP-3) and aggrecanase-1 (ADAMTS-4) have been shown to play a primary role in the degradation of proteoglycans.[65] Most studies on MMP inhibitors are related to rheumatoid arthritis,[66] but their mechanism of action might help degenerative arthritis treatment as well.[67] Doxycycline has been shown to inhibit MMP activity, and is currently being investigated as a disease-modifying agent in OA, but is still not recommended for clinical use.[68]

Stem Cells

Stem cells are capable of long-term proliferation, self-renewal, and differentiation into many cell types and lineages. Because of their proliferative potential, stem cells are implicated as being capable of providing tissue repair and regeneration. Stem cells may be classified as embryonic or nonembryonic (somatic or adult) stem cells.

Embryonic stem cells are derived from embryos and have the potential to proliferate without differentiating. The regulatory and governmental restrictions regarding

embryonic stem cells limit research, as well as the further involvement of these cells for intra-articular injections. Induced pluripotent stem cells (iPSCs) are derived from a nonpluripotent cell (adult somatic cell) by "reprogramming" the cells by transfection with specific genes.[69] The iPSCs have similar functional capability as embryonic stem cells and, as they are developed from a patient's own somatic cells, they may not lead to a significant immunogenic response.[69]

Adult stem cells are undifferentiated cells found among differentiated cells in a tissue or organ; these represent a progenitor cell population with multipotent potential.[70] Adult stem cells do not have the plasticity of embryonic stem cells, but they may differentiate into multiple lineages of their tissue of origin or undergo significantly more replicative cycles than other cells. Adult stem cells found in the bone marrow are classified either as hematopoietic stem cells and bone marrow stromal stem cells (or mesenchymal stem cells [MSCs]).[70] The hematopoietic stem cells form all types of blood cells, whereas the adult MSCs differentiate into different mesenchymal tissues, which include bone, tendon, cartilage, fat, or muscle. Neural stem cells, epithelial stem cells, and hematopoietic stem cells are not currently a focus for musculoskeletal applications, as MSCs are the main cell type being investigated for treatment of OA.[70,71]

One of the main questions in the use of stem cells is how to identify exactly how cells differentiate and to identify the fate of these cells in the target tissue. Under appropriate culture conditions, MSCs are capable of differentiating into the osteogenic, chondrogenic, myogenic, and adipogenic lineages.[72,73]

Safety issues are usually discussed regarding stem cell therapy. Centeno and colleagues[74] recently published a 339 patient surveillance study with no neoplastic complications. In this study, the average follow-up was 11.3 months and the maximum follow-up was 4 years. Wakitani and colleagues[75] reported that 41 patients received MSC autologous implantations with no carcinogenic or infection complications after an average follow-up of 75 months (range 5–137 months).

Stem cells may be used clinically in cell suspension, as concentrates, or expanded by culture.[73,76] They can be delivered through knee injections or combined with surgical procedures.[73] Several MSC cell sources have being evaluated for cartilage repair, including cells derived from bone marrow,[77] periosteoum,[77] synovial tissue,[78,79] adipose tissue[80] and infrapatellar fat-pad.[81] Emadedin and colleagues[82] described a case series of 6 female patients who had received intra-articular injection of MSCs. The MSC samples were obtained by bone marrow aspiration and isolated in the laboratory. The investigators described increases in cartilage thickness as well as decreases in subchondral bone edema. Centeno and colleagues[83] reported cartilage growth in one patient following cultured bone-derived MSC injection. Pak[84] reported 2 patients older than 70 years with knee OA treated with MSC injections resulting in a reduction of knee pain.

Synovial-derived stem cells are described as the tissue-specific cells for cartilage regeneration.[79,85] Koh and colleagues[86] described a case series of 18 patients who received intra-articular injections of adipose synovium-derived autologous mesenchymal stem cells for treatment of OA. The investigators described that the injections reduced knee pain, improved knee function, and improved cartilage score on MRI evaluation. Davatchi and colleagues[87] reported 4 patients with moderate to severe OA treated with cultured bone marrow–derived MSCs (BMMSCs) that demonstrated clinical improvement at 6-month follow-up.

Umbilical cord cells and fetal stem cells would seem to have tremendous potential for cartilage repair.[88,89] However, to date there is very little information available. These cell sources may be viable option from a biologic perspective, but clinical use will require further research, consideration of ethical issues, and changes in the regulatory environment.

The resultant cartilage degeneration after partial menisectomy has led to clinical trials examining the safety and efficacy of single intra-articular stem cell injections. These injections can vary widely and usually differ in human MSC (hMSC) concentration and injection vehicle make-up. Ongoing OA studies to determine the most effective use of hMSCs have used methods of cell delivery such as suspension in commercial sodium hyaluronan or diluted hyaluronan.[90]

Currently there is lack of clinical reports on stem cell injections in the knee. Most studies have evaluated cells used at the time of cartilage repair surgical procedures. MSCs have been evaluated for treatment of focal articular cartilage defects using 1-step MSC isolation from bone marrow concentrates or using cultured MSCs.[75] MSC implantation technique and cartilage lesion debridement is similar to autologous chondrocyte implantation surgery in the treatment of focal chondral lesions.[75,91,92] Buda and colleagues[91] described technical aspects of the surgical treatment of osteochondral lesions in the knee with MSC as a single-step procedure.[91] This procedure involves aspirating bone marrow before the surgical procedure, separating BMMSCs by centrifugation, and injecting them into the cartilage defect using a scaffold.[91] In 2004, Wakitani and colleagues[93] reported 2 patients treated with cultured BMMSCs for full-thickness patella cartilage lesions. Nejadnik and colleagues[94] reported their results comparing a cohort of 36 patients treated with autologous chondrocyte implantation (ACI) and a cohort of 36 patients treated with cultured BMMSC. The investigators reported no statistically significant difference between the 2 treatments in functional evaluation. The investigators also obtained biopsies of 7 patients (4 in the BMMSC group and 3 in ACI group) during second-look arthroscopy demonstrating hyalinelike cartilage in both. Potentially, these approaches may even be used to treat early unicompartmental arthritis with normal subchondral bone.[95,96]

Gene Therapy

Gene therapy is the process of genetically modifying cells to alter the expression of one or more genes in an effort to exert a therapeutic effect. Gene therapy can be administered directly to an organism (in vivo) or to explanted cells or tissues that can then be reimplanted or injected (ex vivo).[45,97] A vector carrying the gene of interest is loaded into the cell. This process inserts the new genetic material (DNA) into the cell to induce expression of the desired transgenes.[45] Theoretically, gene therapy in the knee offers the benefit of the exposure being restricted to the local intra-articular space, which not only avoids systemic side effects but also should provide a longer-lasting effect.[45] The synovial cells are possibly the easiest target cells for intra-articular transgene expression, as they are largely available and accessible inside the knee.

Clinical use of gene therapy in the knee seems to be a more distant reality because of the several clinical safety trials that are needed before widespread clinical use. Ha and colleagues[98] have performed a phase I safety study of retroviral transduced human chondrocytes expressing transforming growth factor-beta-1 in degenerative arthritis patients, and they reported no safety issues. Animal model studies have illustrated both the potential positive and potential negative effects of gene therapy. Hsieh and colleagues[99] demonstrated that thrombospodin-1 might suppress OA progression in a rat model experiment.[90] On the other hand, Watson and colleagues[100] demonstrated knee arthrofibrosis after adenovirus injection to overexpress TGF- β1 in rat knee joints. Additional intracellular and extracellular growth and differentiation regulators that may serve as suitable constituents include parathyroid hormone–related protein,[101] Indian Hedgehog,[64,102] retinoic acid,[103–105] wnt-β-catenin,[106,107] SOX9,[108–111] CART-1,[112,113] and runt.[114]

Gene therapy may be the most promising treatment for long-term cytokine delivery into the knee.[45] However, further study is required, and gene therapy techniques are not expected to be clinically available in the short term.

FINAL CONSIDERATIONS

Our protocol is to start with a corticosteroid injection if there are any signs of active synovitis or effusion. If the symptoms are rather just chronic, activity-related pain with no evidence of an effusion, we may consider HA injection as the first-line treatment, because of the potential for HA to provide longer duration of relief. On occasion, combined injection of a corticosteroid and HA may be considered, and appears to be safe. PRP or autologous conditioned serum is uncommonly used in our current treatment protocol, based on the variability in different preparations, modest reported efficacy, and cost. We do not currently recommend injections in a prophylactic manner, given the lack of any evidence that any injectable substance can affect the structure and/or composition of articular cartilage. Perhaps in the future, substances such as lubricin-mimetics or substances that affect production of proinflammatory mediators, MMPs, or other catabolic factors may have a role in prevention of posttraumatic arthrosis. Stem cell injections are not currently used in our practice for nonoperative treatment of the injured joint. Stem cell approaches will be a more viable approach in the United States once the Food and Drug Administration guidelines allow culturing and manipulation of autologous cell aspirates.

In the future, knee injections may be used as a nonsurgical approach, as well as associated with surgical procedures. Currently most approaches are symptom-modifying, based on providing pain relief and improvement of symptoms, but certainly future approaches will aim to be structure-modifying or even regenerative treatments.

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