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Intra-articular Treatment of Knee Osteoarthritis: from Anti-inflammatories to Products of Regenerative Medicine

Masters M. Richards, MD¹, Joshua Shane Maxwell, DO³, Lihui Weng, PhD¹, Mathew G. Angelos², and Jafar Golzarian, MD¹

¹University of Minnesota-School of Medicine, Department of Vascular and Interventional Radiology 420 Delaware St. SE, Minneapolis, MN 55455, Ph. (612)626-5388

²University of Minnesota-School of Medicine, Department of Hematology, Oncology, and Transplantation, 401 East River Parkway, Suite 131, MMC 194, Minneapolis, Minnesota 55455, Ph. (612)625-3654

³University of Minnesota-School of Medicine, Department of Family Medicine and Community Health, 420 Delaware St. SE, MMC 381, Minneapolis, MN 55455, Ph. (612)625-0646

Abstract

Objectives—Knee osteoarthritis (OA)¹ is a debilitating condition that may ultimately require total knee arthroplasty (TKA)². Non-operative treatments are bracing, oral analgesics, physical therapy, and intra-articular knee injection (IAKI)³. The objective of this paper is to provide a systematic literature review regarding intra-articular treatment of knee OA and insight into promising new products of regenerative medicine that may eventually have a substantial effect on treatment.

Methods—A literature search was executed using Medline, Cochrane, and Embase with keywords "knee osteoarthritis" and "injection." Specifically, articles discussing intra-articular knee

¹OA: Osteoarthritis

²TKA: total knee arthroplasty

³IAKI: Intra-articular knee injection

⁴PRP: platelet-rich plasma

⁵MSC: mesenchymal stem cells

Corresponding Author: Joshua Shane Maxwell, DO, 420 Delaware St. SE, MMC 381, Minneapolis, MN 55455, Office ph: 612-625-0646, Mobile ph: 615-714-3350, Maxwe184@umn.edu.
(rich0693@umn.edu), (wengx021@umn.edu), (angel155@umn.edu), (jafar@umn.edu)

Author contributions: Masters MacMillan Richards, MD, resident physician, University of Minnesota department of vascular and interventional radiology: literature search, writing and revising manuscript

Joshua Shane Maxwell, DO, fellow physician, University of Minnesota department of family medicine and community health: writing and revising manuscript; submission of manuscript

Lihui Weng, PhD, assistant professor, University of Minnesota department of vascular and interventional radiology: writing and revising manuscript

Mathew G. Angelos, MD/PhD candidate, University of Minnesota, school of medicine, department of hematology, oncology, and transplantation: writing and revising manuscript

Jafar Golzarian, MD, assistant professor, University of Minnesota department of vascular and interventional radiology: revision of manuscript; project manager, staff physician advisor

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injection using corticosteroids, hyaluronic acid, analgesics, local anesthetics, and newer products of regenerative medicine, such as platelet-rich plasma (PRP)⁴ and mesenchymal stem cells (MSC)⁵, were analyzed.

Results—Forty-five publications were scrutinized. Of these, eleven were level 1, three were level 2, twelve were level 3, two were level 4, and seventeen were level 5. Papers included animal models. Local anesthetics have potential side effects and may only be effective for four hours. Morphine and ketorolac may provide significant pain relief for 24 hours. Corticosteroids may give patients weeks to one months of effective analgesia, but complications may occur, such as systemic hyperglycemia, septic arthritis, and joint degradation. Hyaluronic acid is a natural component of synovial fluid, but efficacy with respect to analgesia is controversial. Platelet-rich plasma formulations, autologous conditioned serum, autologous protein solution, and mesenchymal stem cell injections contain anti-inflammatory molecules and have been proposed to attenuate joint destruction or potentially remodel the joint.

Conclusions—Currently, knee OA treatment does not address the progressively inflammatory environment of the joint. More investigation is needed regarding products of regenerative medicine, but they may ultimately have profound implications in the way knee OA is managed.

Keywords

Knee osteoarthritis; Injection; Corticosteroids; Hyaluronic acid; Products of regenerative medicine

Introduction

Osteoarthritis (OA) is the most common sub-type of arthritis and represents a major burden on public health in the world. More specifically, OA of the knee involves the largest synovial joint in humans [1]. Knee OA is especially prevalent in middle-aged and elderly patients. As of 2012, knee OA affected more than 46 million Americans. Radiographically, the prevalence was estimated to be 27% of patients under seventy years old and 44% of patients over eighty years old [2]. Worldwide, prevalence is estimated at more than 250 million patients [3].

Risk factors for knee OA include increased age, obesity, trauma to the joint, postmenopausal female status, joint malalignment, and some genetic characteristics [4]. OA involves the cartilage, subchondral bone, ligaments, periarticular structures, and menisci. Cartilage degradation and bone remodeling are characteristic pathological features observed in patients with OA [5].

In this systematic review of the literature, we highlight the current treatment methods of knee OA, including oral analgesics, intra-articular corticosteroid injection (IACI), and hyaluronic acid and explore a potentially promising new treatment option using image-guided intra-articular injection. The products of regenerative medicine subsequently discussed, including platelet-rich plasma and mesenchymal stem/stromal cells, offer promise in treating OA because they address the concept of joint remodeling, rather than anti-inflammatory mechanisms.

Materials and Methods

A literature search was performed using the keywords “knee osteoarthritis” and “injection.” More specifically, articles discussing intra-articular knee injection using corticosteroids, hyaluronic acid, and the newer products of regenerative medicine, such as platelet-rich plasma (PRP)⁶ and mesenchymal stem cells (MSC)⁷, were analyzed.

Medline, Cochrane, and Embase databases helped to ultimately focus on forty-five publications on the subject. Other joints that are prone to osteoarthritis, such as the glenohumeral and femoral-acetabular joints were excluded. Animal models of knee osteoarthritis were examined, as well as limited human pilot trials. The vast majority of papers studied were from 2009-2014. Publications prior to 2003 were excluded. The literature search mainly focused on the clinical aspects of knee osteoarthritis, but basic science publications were also examined, including studies investigating the immunological aspects of the knee joint space and animal models. Of the 45 papers ultimately selected eleven were level 1, three were level 2, twelve were level 3, two were level 4, and seventeen were level 5.

Theory

The specific pathophysiology of OA is complex; inflammatory cytokines and proteolytic molecules have been implicated and represent the primary substances contributing to this disease [4]. Other inflammatory compounds, including Interleukin-1 (IL-1), IL-6, IL-8, IL-15, IL-17, IL-21 tumor necrosis factor-alpha (TNF- α), and leukemia inhibitory factor (LIF) are also responsible in part for OA [4]. Moreover, proteolytic enzymes such as the matrix metalloproteinases (MMP) and aggrecanase-1, contribute to collagen and joint extracellular environment proteoglycan destruction, respectively [6]. In addition, A-disintegrin, thrombospondin-1, oxide synthase 2, cyclooxygenase (COX-2), and prostaglandin E contribute to joint inflammation and, ultimately, destruction [4]. Meanwhile, there appears to be a counter-regulatory mechanism in place. Anti-inflammatory and anabolic molecules localized to the joint microenvironment include insulin-like growth factor 1 (IGF-1), transforming growth factor beta (TGF- β), fibroblast growth factor 18 (FGF-18), IL-4, IL-10, and platelet derived growth factor (PDGF) [6].

The treatment goals for patients with knee OA are to decrease pain, improve joint mobility, and decrease functional impairment [7]. Current treatment regimens predominantly focus on controlling pain and inflammation. However, recent studies have implemented novel, cell based therapies that have the potential to structurally remodel the knee joint at a biochemical level, contributing to anabolic effects on bone and cartilage. Treatments for knee OA vary on a spectrum, with exercise and weight loss representing the non-interventional side, to total knee arthroplasty on the opposite end. In the middle of this spectrum is intra-articular knee injection. Historically, corticosteroids and hyaluronic acid have been the most commonly utilized intra-articular treatments [6]. Products of regenerative medicine, including

⁶PRP: platelet-rich plasma

⁷MSC: mesenchymal stem cells

mesenchymal stem/stromal cells, platelet rich plasma, and autologous conditioned serum (ACS), as well as other agents such as intra-articular morphine demonstrate promise in treating pain and joint damage in knee OA [8]. Additionally, botulinum toxin has been studied against corticosteroids in a prospective, double-blinded randomized controlled trial with results suggesting a possible role in treating this disease [9].

Results and Discussion

Conservative (Non-interventional) Treatment

Weight loss is the first recommendation made for patients with knee OA. Acetaminophen is the first line drug endorsed by the American Geriatric Society and non-steroidal anti-inflammatory drugs (NSAIDs) are generally preferred by orthopedists [7]. Acetaminophen is relatively inexpensive and generally well-tolerated, though has been associated with hepatotoxicity in some individuals [7]. Additionally, chronic use of acetaminophen may lead to anion-gap metabolic acidosis from 5-oxoproline by-products. This is due to glutathione and cysteine depletion with upregulation of an enzyme in the gamma-glutamyl cycle. Acetaminophen levels may be therapeutic or low in these patients; 5-oxoproline assays are not available at every institution, which may make diagnosis more difficult [10]. NSAIDs have a concerning side-effect profile as well, including renal insufficiency, gastritis, and peptic ulcer formation. Additionally, there is the potential for rare adverse effects involving the cardiovascular and cerebrovascular systems with continued NSAID use [7].

Analgesia

Steroids and hyaluronic acid have been administered as intra-articular injections for analgesia in the treatment of knee OA for some time. In the 1980's and 1990's, basic science research demonstrated that opioid receptors exist not only in the central nervous system, but also in peripheral tissue, such as joint capsules [8]. This discovery led to the investigation into intra-articular administration of narcotics, such as morphine. In fact, ketorolac (an NSAID), morphine, and local anesthetics, such as bupivacaine and ropivacaine, have been given intra-articularly following orthopedic surgery procedures, such as arthroscopy. Several studies have commented on side effects of sodium channel antagonists, even when administered into the joint. Potential adverse effects include allergic reactions, perioral anesthesia, convulsions, and hemodynamic instability [8]. Breu, et. al studied the destructive effects of the local anesthetics bupivacaine, ropivacaine, and mepivacaine on both normal and osteoarthritic human chondrocytes. Immunohistochemical and flow-cytometry demonstrated increased cell death, apoptosis, necrosis, and caspase activation in chondrocytes, with the osteoarthritic cells more severely affected [11]. Furthermore, local anesthetics may only provide up to four hours of pain relief [12].

A randomized controlled trial in 2006 by Ng et. al, compared 63 patients administered bupivacaine (B group), ropivacaine (R group), or ropivacaine plus morphine and ketorolac (RMK group) as an intra-articular injection following knee arthroscopic procedures [12]. The patients were monitored for one week with recordings of rest pain, activity pain, ability to perform activities of daily living, and dosage of rescue medications consisting of tramadol and acetaminophen. The combination drug (ropivacaine, morphine, and ketorolac) group had

a statistically significant decrease in visual analogue score from 8-24 hours post-injection compared to the other two groups ($p < 0.05$). In the same group, more patients went back to work on post-operative days one and two [12].

Intra-articular Corticosteroid Injections (IACI)

The first clinical trial of intra-articular corticosteroid injection was pioneered by White and Norton in 1958 and is now endorsed by the American College of Rheumatology [13]. These injections are typically administered by rheumatologists, orthopedic surgeons, and primary care physicians in an outpatient setting [14]. Steroid injections may be indicated after failing NSAIDs and acetaminophen, but some researchers suggest only using them once every three months for a maximum of two years due to negative potential side effects [7].

The mechanism underlying the anti-inflammatory efficacy of corticosteroid is multifactorial, but generally involves blocking antigen opsonization, leukocytic cell adhesion, and cytokine diapedesis within the capillary endothelium [13]. Corticosteroids also attenuate the effects of IL-1, decrease leukotriene and prostaglandin release, and inhibit metalloproteases and immunoglobulin synthesis [13]. The specific corticosteroids used vary by the physician's preference, but generally include triamcinolone, betamethasone, and methylprednisolone [1].

The duration of action of intra-articular corticosteroid injections remains controversial, with various studies quoting anywhere between 1 to 24 weeks. There is consensus that steroids provide relief to patients for approximately one week after injection. However, in Hepper, et. al's recent review article of level I evidence investigating efficacy of steroids versus placebo injections, there was no difference in visual analogue score pain values between experimental and control groups three to four weeks after treatment [15]. Other studies have compared pain relief from corticosteroids to hyaluronic acid injections. It is suggested that there is an immediate benefit to use corticosteroids, i.e. lasting approximately one week, while hyaluronic acid may provide some analgesia that begins only after approximately four weeks [16].

Adverse effects of corticosteroid injections do exist, however. Handler and Wright first described radiographic evidence of destruction of the knee joint and cartilage after several corticosteroid injections [1]. The incidence of joint infection following corticosteroid administration is rare, but may be as high as one in three thousand patients, with an associated mortality rate of approximately 11%. Additional known complications include pain, skin atrophy, tendinopathy, and systemic hyperglycemia [14].

Intraarticular Hyaluronic Acid Injection

Aside from steroids, the most commonly injected drug currently used to treat knee OA is hyaluronic acid (HA), a glycosaminoglycan composed of beta-glucuronyl and beta-acetylglucosamine [7]. It is found naturally on the upper 1-2 micron layer of human cartilage and is the main component of the synovial fluid [2]. Hyaluronic acid is secreted by type B synoviocytes, chondrocytes, and fibroblasts [7]. In an osteoarthritic knee joint, the molecular weight of HA in the synovial fluid has been found to decrease by as much 33-50% [7]. It is proposed that HA improves joint elasticity, viscosity, and shock-absorption [13]. The true mechanism of action is not well understood, however.

Mechanistically, HA may be involved in attenuating phagocytosis, as well as decreasing prostaglandin, fibronectin, and cyclic adenosine monophosphate levels. It is also hypothesized that HA prevents the release of arachidonic acid, blocks nociceptors, and reduces the formation of bradykinin and substance P [7].

HA, also known as viscosupplementation, received FDA approval in 1997 for treatment of OA in the United States. It is a drug, but technically classified as a medical device for the purposes of satisfying FDA requirements in its treatment context. Although studied extensively, the efficacy of HA is questionable and possibly transient. Based on the proposed pathophysiology and mechanisms of the drugs used in OA injections, some researchers have suggested using corticosteroids exclusively in joints with effusions, while “dry” joints might benefit from HA [13]. Like corticosteroids, there have been numerous randomized controlled trials assessing the efficacy of HA compared to placebo injections. In 2009, the American Academy of Orthopaedic Surgeons (AAOS) conducted a meta-analysis regarding HA’s treatment outcomes before publishing their clinical practice guidelines (CPG). The evidence for efficacy was considered inconclusive. As of early 2014, the AAOS did not find adequate evidence to support listing HA as indicated for treatment of knee OA [7]. However, Bannuru et. al’s 2015 meta-analysis analyzed a total of sixty-eight publications involving hyaluronic acid and determined that this drug was superior to both oral acetaminophen and oral placebo. Hyaluronic acid also appears to be more effective than intra-articular placebo, which may be due to attenuation of peripheral nociceptors [3]. Also, Henrotin et. al conducted a recent meta-analysis regarding consensus on viscosupplementation. The authors concluded that the drug is indicated in treating mild to moderate osteoarthritis of the knee. Viscosupplementation’s side effects are well-tolerated by patients. Contrary to American Geriatric Society guidelines, viscosupplementation is not necessarily only indicated after failing acetaminophen and NSAID drugs, the former of which is considered first-line treatment by the organization [17]. Adverse events from this treatment are rare and generally include self-limiting synovitis, hemarthrosis, muscle pain, and pseudogout [13].

Autologous Conditioned Serum (ACS)

A primary concern consistently raised in the treatment of knee OA with the aforementioned standard therapies is that current treatments target the inflammation and pain, rather than potentially reversing and correcting the underlying disease process.

As mentioned previously, IL-1 is a major contributory player causing inflammation in knee OA. This cytokine stimulates chondrocytes and synovial fibroblasts to upregulate matrix metalloproteinases, thereby damaging joint cartilage [18]. Therefore, IL-1 blockade may offer some benefit. Autologous conditioned serum (ACS) delivery using intra-articular knee injection was discovered in the mid-1990’s due to its high concentrations of endogenous IL-1 receptor antagonist (IL-1Ra) [19]. The concentration of IL-1 receptors is higher in tissue such as synovial fibroblasts and chondrocytes affected by OA. The Orthokine™ method ultimately generates fluid with approximately 140 times the IL-1Ra concentrations compared to normal, physiologic serum. Additional anti-inflammatory cytokines and growth factors in autologous conditioned serum include TGF-B, PDGF, IGF-1, IL-4, and IL-10 [18]. Another product of regenerative medicine and IL-1 receptor antagonist

compound, autologous protein solution, has been described by O'Shaughnessey, et. al [20]. This was developed from the serum of patients with radiographic-proven osteoarthritis. Anti-inflammatory compounds isolated by immunosorbent assay in addition to IL-1 Ra include sIL-1RII, sTNF-RI, and sTNF-RII [20]. ,

Autologous conditioned serum was recently studied in a randomized controlled trial, which compared it to hyaluronic acid and a saline placebo group [18]. A total of 376 patients were randomized to these treatments and evaluated with Western Ontario and McMaster University Osteoarthritis index (WOMAC) (Figure A) and visual analogue (VAS) pain scales (Figure B) at 7, 13, and 26 weeks after injection. The VAS scores at each clinical evaluation were lower in the autologous conditioned serum group compared to the other two groups, with a statistically significant difference ($p < 0.001$). However, there was no significant difference in the VAS scores between the hyaluronic acid and saline groups statistically ($p > 0.05$) [18]. Adverse events included localized pain, swelling, or joint effusion and did not appear to be significantly different between the three groups [18].

Autologous conditioned serum and autologous protein solution are promising for several reasons. First, they utilize the patient's own serum and cytokines, so there is no immune response against a foreign source. Second, they appear to be safe, based on the studies available. Third, they may be efficacious in the treatment of knee OA.

Platelet Rich Plasma

Another product of regenerative medicine, platelet rich plasma (PRP), has received attention in recent clinical trials for treating knee OA. PRP is plasma with significantly higher platelet concentrations, as well as its associated growth factors, as compared to physiologic plasma. The concentration of platelets in the PRP solution is generally 4-6 times the patient's baseline concentration [21]. Unfortunately, preparations of platelet rich plasma vary considerably. Leukocyte-rich and leukocyte-poor variations can be produced in the laboratory [22]. The growth factors typically present in the various solutions typically include IGF-1, PDGF, and TGF- β [6]. According to Braun, et. al, a recent meta-analysis concluded that 71% of PRP studies showed some degree of anabolic effects on chondrocytes, such as type II collagen deposition. However, only 4.8% of studies clearly specified the formulations of PRP utilized, such as red blood cell, white blood cell, and platelet concentrations [22]. Given that cytokine levels vary with leukocytes, this makes comparing different formulations quite difficult, especially with respect to clinical efficacy in treating knee osteoarthritis. These growth factors can be found in the alpha bodies within platelets. IGF-1 has anabolic effects in the joint, encouraging formation of type II collagen, proteoglycans, and other extracellular matrix components. These elements can promote adhesion between chondrocytes and discourages proteolysis of the extracellular matrix microenvironment. PDGF stimulates production of chondrocytes and TGF- β appears to have anabolic effects on chondrocytes, the latter of which is not well understood. PRP also seems to be beneficial in attenuating pro-inflammatory cytokines, such as nuclear factor (NF) κ -B and IL-1 [6]. Additionally, TGF- β further promotes the differentiation of articular mesenchymal stem/stromal cells into chondrocytes [23].

One of the first clinical applications of PRP was an effort to treat blood loss following open heart surgery in 1987 [24].

Like other products of regenerative medicine, PRP has gained notoriety recently as a potentially efficacious new treatment option for knee OA. A 2014 randomized controlled trial enrolled thirty-one patients treated with PRP versus thirty-one patients prescribed an exercise regimen. The WOMAC pain scores were used to evaluate all patients and were noted to be lower in both groups at six months from initial treatment. The experimental PRP group had WOMAC pain scores that were significantly lower than the control group ($p < 0.05$). Interestingly, break-through acetaminophen consumption was higher in the PRP group. The researchers attributed this to injection-related pain three to seven days after administration and was thought to be self-limited [21].

Recently, three meta-analyses have been published supporting the efficacy of PRP in the treatment of knee OA. Chang et al., analyzed 16 studies involving 1543 patients and found that PRP was superior to HA with respect to pain control. PRP's beneficial effects may last up to one year and are more pronounced in patients with mild OA. Steroids were found to only be effective for up to one month and HA for two months [25]. Khoshbin et al., examined four randomized controlled trials and two prospective non-randomized studies, with a total of 577 patients. PRP appeared to be more effective than HA and normal saline placebo in pain relief based on WOMAC, but not VAS [26]. Tietze, et al, reviewed twelve studies regarding PRP in the treatment of OA. These researchers concluded that PRP was efficacious based on functional international knee documentation committee (IKDC) scores and VAS pain scores, especially when compared to hyaluronic acid, but there may be a publication bias. Also, these benefits may be increased in patients under age fifty and those with pathology limited to the cartilage tissue. Moreover, they found there were more adverse effects with PRP when the solution was prepared with double centrifugation technique, as compared to the single method [24]. Adverse events were minor, including injection site pain, joint stiffness, syncope, dizziness, headache, nausea, gastritis, sweating, and tachycardia [26]. Pain control with PRP appears to begin around two months following injection and may last 6 to 12 months [24].

Intra-articular Mesenchymal Stem/Stromal Cell (MSC) Injection

An additional product of regenerative medicine, mesenchymal stem/stromal cells (MSC), has been hypothesized as a treatment for knee osteoarthritis [28]. Bone marrow mesenchymal stem cells (BM-MSC's) are considered to be multipotent, which allows them to differentiate into several cell lineages, including type II chondrocytes, adipocytes, and osteoblasts/osteocytes [27]. Bone marrow mesenchymal stem cell studies thus far have been performed in the context of animal models and small human pilot trials (Table A). Traditionally, mesenchymal stem cells are derived from autologous iliac crest samples, but have been shown to be also isolated from adult (skeletal muscle, synovium, adipose tissue) and embryonic (umbilical cord) sources [29]. While there remains some controversy with respect to a *bona fide* identification of human mesenchymal stem cells, two generalized and commonly implemented properties include: 1) long-term adherence to tissue culture plastic

surfaces, and 2) immunophenotypically defined by expression of a variety of cell surface antigens, such as CD73, CD105, CD146, and STRO-1 [30]

Mesenchymal stem cells provide several key advantages over the current treatments for translational OA therapy. First, due to the autologous nature of these cells, autoimmune rejection risk is eliminated. Second, mesenchymal stem cells can be isolated in relatively high quantities and with excellent purity, thus optimizing the potential for differentiation into target tissue of the damaged joint space [31]. Third, like other products of regenerative medicine, it has been well documented that mesenchymal stem cells possess robust anti-inflammatory properties in that they express IL-1 Ra and can directly antagonize resident macrophages of the joint space from secreting pro-inflammatory cytokines [30,32]. Fourth, human mesenchymal stem cells can be cultured and expanded *ex vivo* using Good Manufacturing Practices (GMP), offering the opportunity for additional pharmacological treatment to enhance cell proliferation/maturation, as well as their repair potential [33]. Lastly, mesenchymal stem cells have been utilized in human clinical trials over the past ten years for widespread application, which demonstrates they are a safe and effective method for translational therapies [34].

Recent animal models have investigated certain growth factors, such as TGF-beta and IGF-1, which may promote further remodeling of the diseased joint. In fact, culturing bone marrow mesenchymal stem cells in a medium rich in these factors has been proven to generate the natural joint environmental components of type II collagen, decorin, chondroadherin, cartilage oligomeric matrix protein, fibromodulin, aggrecan link protein, and other proteoglycans [35]. In addition, the compound Kartogenin has also been studied in mouse models, which facilitated bone marrow mesenchymal stem cell differentiation into type II chondrocytes and secretion of accompanying extracellular matrix [27].

A recent sheep model by Al Faqeh et al., has shown intriguing results [35]. In this study, 16 sheep underwent surgical excision of the anterior cruciate ligament and medial meniscectomy. The sheep were then forced to exercise in order to cause OA. Three weeks post-operatively, the injections occurred with one group receiving mesenchymal stem cells + anabolic growth factors, another experimental group receiving mesenchymal stem cells, and the control group receiving stem cell culture media. The International Cartilage Repair Society (ICRS) assessment scores were used to objectively compare the three groups' gross and histological joint specimens after the animals were sacrificed. There was gross evidence of partial meniscus and cartilage regeneration in the group treated with stem cells and growth factors. The stem cell only group had minor gross cartilage regeneration, with scarring of the damaged meniscus. The control group did not demonstrate improvement. The two experimental group's international cartilage repair society scores decreased in a statistically significant manner, as compared to the control group. This indicated partial reversal of damage and inflammation. However, there were no significant differences between the two experimental groups, [35].

Orozco, et al, performed a prospective study of twelve human patients treated with mesenchymal stem cells [36]. The VAS improved from baseline two years following injection. The poor cartilage index also significantly decreased from baseline. There was

qualitative improvement in MRI's of the joint, but this did not reach statistical significance [36]. Ahmad et al, investigated clinical and MRI changes of ten patients treated with intra-articular injection of peripheral blood stem cells (PBSC) [37]. The WOMAC pain scales decreased 29% from baseline at one year and were considered statistically significant. MRI was performed at baseline and at one year, which revealed an increase in cartilage deposition in 65/160 joint compartments studied. Adverse effects included pain and edema, which were self-limiting [37]. It is worth noting that the existing human trials are limited and that further investigation is needed regarding treatment with stem cells.

Conclusions

Osteoarthritis of the knee joint is a common condition that affects more than a quarter of a billion patients worldwide and constitutes a significant burden on health care systems, with respect to finances and morbidity. The current treatment model revolves around treating pain and decreasing inflammation with oral and intra-articular medications with possible subsequent surgical arthroplasty. Presently, there are no treatment methods widely available to reverse the destructive process involving joint inflammation. In recent years, products of regenerative medicine, such as platelet-rich plasma, autologous conditioned serum/ autologous protein solution, and mesenchymal stem cells, have approached the treatment of knee OA in a much different way. The goal is to reverse the inflammation and to transition the joint to an anabolic, rather than catabolic, state. This may allow the joint to remodel itself and to ultimately heal, resulting in decreased pain, increased mobility, and potentially avoiding stressful surgery. More basic science research and, eventually, human clinical trials will be required to investigate this possibility.

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⁴ Hennepin County Medical Center Library, 701 Park Avenue, Minneapolis, MN 55415

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Pain
How much pain do you have
Walking on flat surface
Going up or down stairs
At night while in bed
Sitting or lying
Standing upright

Stiffness
How severe is your stiffness after first wakening in the morning
How severe is your stiffness after sitting, lying, or resting later in the day

Function
What degree of difficulty do you have
Descending stairs
Ascending stairs
Rising from sitting
Standing
Bending to floor
Walking on flat
Getting in/out of car
Going shopping
Putting on socks/stockings
Rising from bed
Taking off socks/stockings
Lying in bed
Getting in/out of bath
Sitting
Getting on/off toilet
Heavy domestic duties
Light domestic duties

Figure A. Western Ontario and McMaster University Osteoarthritis Index (WOMAC) questionnaire (with permission from Roos, et. al)

Figure B. Visual Analogue Scale (VAS) (with permission from Erdek, et. al)

Table A
Comparison of animal models of knee osteoarthritis treated with mesenchymal stem cells

STUDY	ANIMAL SPECIES	ARTHRITIS INDUCTION METHOD	STEM CELL SOURCE	OUTCOMES	LABELLING METHOD OF STEM CELLS
FRISBIE [41]	Horse	Arthroscopic instrumentation of middle carpal joint (osteocondral fragment)	Equine bone marrow derived mesenchymal stem cells (MSC's)	Prostaglandin E2 (PgE2) levels; range of motion; synovial WBC count; TNF levels; gross/histological analysis	n/a
HUURNE [38]	Mouse	Injection of type VII collagenase	Adipose derived stem cells (around inguinal lymph nodes)	Histology analysis; formation of enthesophytes	Green fluorescent protein
DIEKMAN [42]	Mouse	10 N pre-load fracture under sedation	Mouse mesenchymal stem cells	Serum and synovial cytokines; IHC microscopy	Chloro methylbenzamido (CM-Dil)
HORIE [43]	Rat	Hemi-meniscectomy	Marrow-derived human MSC's	Gross, IHC, microscopic analysis	Cm-Dil
SATO [44]	Guinea pig	Spontaneous cartilage degeneration	Human MSC's	Gross photos; IHC analysis of type II collagen	Carboxy fluorescein diacetate succinyl ester
MURPHY [45]	Goat	Excision of medial meniscus, ACL resection	Iliac crest MSC's	Microscopic and gross photographic analysis	Green fluorescent protein
AL FAQEH [35]	Sheep	Excision of medial meniscus, ACL resection	Iliac crest bone marrow stem cells	Gross photographs; histological analysis; ACRS assessment	n/a